

THE USE OF INHALED BECLOMETHASONE TO DECREASE  
THE DURATION OF PAROXYSMAL COUGHING IN  
PEDIATRIC PATIENTS WITH PERTUSSIS:  
RESULTS AND METHODOLOGIC ISSUES  
IN A RANDOMIZED CLINICAL TRIAL

CENTRE FOR NEWFOUNDLAND STUDIES

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## **ABSTRACT**

**Purpose:** To determine whether the short-term use of inhaled beclomethasone significantly decreases the duration of paroxysmal coughing in young children with early pertussis, as compared with inhaled placebo.

**Design:** Randomized, double-blind, placebo-controlled clinical trial.

**Subjects:** Subjects were recruited from the outpatient department and microbiology laboratory of the Janeway Child Health Centre. General practitioners and public health nurses in the area were also canvassed for referrals of potential subjects with clinical pertussis. From a total of 210 contacted subjects who met the case definition, 23 were enrolled with 18 staying in the study long enough to provide usable data.

**Method:** Subjects were randomly allocated to receive inhaled beclomethasone or placebo three times daily for 30 days. Cough counts were recorded daily by parents and teachers. The time to cessation of coughing for both groups was considered the primary outcome variable.

Numerous methodological problems were encountered in the design and implementation of this trial. These included difficulties in choosing a primary outcome variable and a corresponding measurement instrument, problems in the assumptions made in the determination of sample size, difficulties with case definitions, and problems with recruitment and retention of subjects. These problems are reviewed in detail and solutions which may be applied to future trials are proposed.

**Results:** Subjects ranged in age from 2 to 95 months. The mean duration of coughing at entry into the study was 14 days. The mean duration of coughing following entry into the study was 26.8 days in the beclomethasone group and 21.4 days in the placebo group ( $p = 0.2$ ).

**Conclusions:** Significant problems were encountered with the recruitment for this study leading to low numbers of subjects being enrolled and a subsequent low power. Such problems have precluded any definite conclusions. However, data suggest that the use of inhaled beclomethasone is not effective in the treatment of patients with pertussis infection and may actually prolong the duration of coughing. Further trials are needed if this question is to be answered. Suggestions for the design and implementation of such a trial, or a trial of other therapies for pertussis, are provided and discussed.



### **Dedication**

**This thesis is dedicated to my wife, Sylvia and our beautiful daughter, Claire, without whose unwavering support, unlimited understanding, unbounded love, and uncontrollable editing, this document would never have materialized.**

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## CHAPTER 1

### Introduction and Background

#### Introduction

Pertussis or "whooping cough" was first described in 1578 by a French physician in Paris, France, following an epidemic in that city during the same year<sup>1</sup>. Today, pertussis continues to be a significant cause of childhood morbidity around the world<sup>2-5</sup>. The disease is caused by the bacterium *Bordetella pertussis*, a small, non-motile, fastidious, gram negative, rod-shaped bacterium which infects humans exclusively. Transmission results from contact with airborne droplets or particles from the respiratory tract of an infected individual. While attack rates vary with immunization status<sup>6</sup>, it has been reported that from 90-100% of susceptible individuals in a household will develop symptoms of pertussis when exposed to an infected household member<sup>2</sup>.

#### *Clinical Manifestations of Pertussis*

Clinically, the disease is characterized by three stages which together last an average of 6 to 8 weeks. After a mean incubation period of seven days the *catarrhal* stage begins. During this stage the patient experiences mainly upper respiratory tract infection symptoms including lacrimation, rhinorrhea, mild cough, conjunctival injection and a low-grade fever. This period usually lasts from 1 to 2 weeks and is followed by the much more bothersome *paroxysmal* stage. The paroxysmal stage is characterized by

increasingly frequent and severe coughs, which often occur in repetitive series. The coughing *paroxysms*, as they are known, may or may not be followed by a sudden massive inspiratory effort. When present, this creates the characteristic "whooping" sound as air rushes by a narrowed glottis. It is from this sound that the disease takes its name. Coughing paroxysms may be accompanied by cyanosis, bulging eyes, salivation, lacrimation or other symptoms, and often occur sequentially, in rapid succession. Coughing episodes are frequently followed by vomiting. The paroxysmal phase usually lasts for 2 to 4 weeks and is the most severe and dangerous part of the illness <sup>1</sup>. Children are often exhausted during this period, and may lose weight to the point of requiring parenteral nutrition due to the incessant vomiting <sup>7,8</sup>. Occasionally, the disease may be complicated with apneas and pneumonia <sup>1,8</sup>. Prolonged coughing may result in tissue hypoxia with subsequent hypoxic damage <sup>1</sup>, or even death <sup>9</sup>.

The final stage of the illness is known as the *convalescent* stage and is marked by a decrease in the frequency and severity of episodes of coughing, whooping and vomiting. While this phase usually lasts for 1 to 2 weeks, coughing can persist for months, and some patients complain of persistent symptoms associated with upper respiratory infections for years afterwards <sup>1</sup>.

*Epidemiology of Pertussis*

While the North American incidence of pertussis infection has decreased significantly since the advent of universal vaccination, both endemic and epidemic pertussis infection continues to occur. Recent years have witnessed a resurgence of the disease even in the immunized population <sup>2,10, 11</sup>. Between 1992 and 1993, 23 deaths were reported as a result of pertussis infection in the United States <sup>9</sup>.

Canada is affected to an even greater degree than the United States (US) with an estimated annual incidence of 10 cases per 100 000 children reported during the 1970's - 1980's <sup>1</sup>. This rate had climbed to 12 cases per 100 000 for the period between 1984 and 1993 <sup>12</sup>, with a high of almost 35 cases per 100 000 reported in 1994 <sup>13</sup>. This compares with a rate of 0.83-1.2 cases per 100 000 in the US <sup>12</sup>. While more recent estimates of disease incidence among children are not available, overall Canadian and Newfoundland incidence rates are provided as Table 1.1 <sup>13</sup>.

Table 1.1 - The Incidence of Pertussis in Canada and Newfoundland (1990-1995)<sup>13</sup>

	CANADA		NEWFOUNDLAND	
YEAR	NUMBER	RATE / 100 000	NUMBER	RATE / 100 000
1990	8030	30.2	11	1.9
1991	2724	10.1	27	4.7
1992	3605	13.2	44	7.6
1993	7396	25.7	39	6.7
1994	10 151	34.7	334	57.3
1995	-	-	96*	16.9*

\*preliminary figures only<sup>14</sup>.

Though Newfoundland appears to have an annual incidence significantly below the national average in all but the final year of complete reporting, it is possible that this represents significant under-reporting. In addition to the culture-positive patients reported in the table, there may be others that are diagnosed clinically by general practitioners or other health professionals working in the community. These patients may never be cultured, thereby excluding their data from the statistics. Such a phenomenon was observed with an enhanced reporting program in Nova Scotia<sup>10</sup>. This study documented a nine-fold increase in pertussis infection when enhanced surveillance was undertaken. Hence, the burden of disease may be significantly greater than it appears.



## **Prevention of Pertussis**

Most of the recent research work in pertussis has focused on prevention through vaccination. From the time that Jenner first gave an injection of cowpox to his one-year-old son in an effort to prevent the more serious smallpox infection <sup>15</sup>, the medical establishment has sought ways to prevent infectious ailments through the use of vaccines. Today, smallpox has been eradicated as a result, and measles has been targeted for the same fate in the next century <sup>16</sup>. While the eradication of pertussis is also a worthwhile goal, such a prospect remains a distant hope with current vaccines. In 1993 pertussis became the “most prevalent vaccine-preventable disease among US children younger than 5 years” and was the cause of 23 reported deaths in that country between 1992 and 1993 <sup>9</sup>. In Canada, similar findings have been reported with outbreaks occurring in the Yukon, Quebec, and Nova Scotia <sup>10, 17-19</sup>.

### ***Whole Cell Pertussis Vaccines***

Currently employed pertussis vaccines are known as *whole cell* vaccines because they are manufactured from the *whole* Bordetella pertussis organism. Under current whole cell vaccine manufacturing practices, the organisms are grown in bulk culture and then harvested. After centrifugation to concentrate them, the organisms, are suspended in a buffered saline solution. The bacteria are then killed or partially detoxified by physical or chemical methods producing a mixture of multiple bacterial

antigens. This mixture is then combined with diphtheria and tetanus toxoids adsorbed to aluminum to produce the widely used “DTP”(diphtheria, tetanus, pertussis) vaccine <sup>20</sup>.

### *Efficacy and Effectiveness of Current Vaccines*

The persistence of clinical pertussis infection relates to problems with vaccine efficacy and vaccine effectiveness. These problems have been detailed by several investigators in the recent past <sup>2, 11, 21, 22</sup>. While the terms are often used interchangeably in the literature, vaccine effectiveness refers to “the ability of an intervention to produce the desired beneficial effect in actual use.” <sup>23</sup>. Consequently, any factors which decrease use of the vaccine, in addition to problems intrinsic to the vaccine itself, will necessarily have an impact on effectiveness. In contrast, efficacy refers to “the ability of an intervention to produce the desired beneficial effect in expert hands and under ideal circumstances.” <sup>24</sup> Efficacy, therefore, is primarily dependent on the inherent properties of the vaccine itself.

Efficacy of the whole cell vaccines currently in use in Canada and the United States is difficult to estimate due to the absence of a gold standard for diagnosis. Efficacy rates are, therefore, dependent on the case definition used to determine infection in the population at risk. This problem is further compounded by the fact that vaccines currently in use were not tested in clinical trials prior to their introduction <sup>21</sup>. Rather, they were compared to former vaccines tested in a large randomized controlled trial conducted in the United Kingdom following World War II <sup>25</sup>. The unit of comparison was the

"mouse protection test," <sup>26</sup> a test to determine the *in vitro* potency of a particular vaccine preparation. The UK trial had shown a positive correlation between the results of the mouse potency test and the clinical efficacy of pertussis vaccines in immunized children. Consequently, the results of this test on the new vaccines were accepted as adequate for licensure <sup>21</sup>.

Subsequent post-marketing studies of the current whole-cell vaccines, while sometimes reported to reflect efficacy, have more accurately estimated effectiveness by looking at the incidence of pertussis in defined populations of partially and completely immunized individuals. The interpretation and comparison of such studies is complicated by differences in vaccine schedules between different countries <sup>27, 28</sup>, differences in vaccine components (eg. the addition of inactivated polio virus vaccines used in some Canadian provinces) <sup>29</sup>, and differences in the settings in which the studies are conducted (communities, homes, schools and child-care centres) <sup>6, 12, 21</sup>. The practical result of these limitations is that the efficacy and effectiveness of whole cell pertussis vaccines currently in use are largely unknown.

Attempts have been made to estimate effectiveness in the immunized populations in several countries, as alluded to above. In Canada, a study by Halperin et al<sup>10</sup> examining the results of enhanced surveillance on the incidence of pertussis in the Nova Scotia population showed an effectiveness of 45% for the Connaught Laboratories quadrivalent vaccine (DPTP). This study defined pertussis as a positive nasopharyngeal

aspirate culture for pertussis or the presence of a cough for more than 1 week with two or more of the following: paroxysms, cyanosis, vomiting or apnea. A subsequent study of Quebec children by De Serres' group <sup>19</sup> showed that in children who had received at least 4 doses of vaccine, vaccine effectiveness was 61% with a 95% confidence interval of 44-72% in child care centres, and 60% with a 95% confidence interval of 10-82% in schools. Pertussis was defined in this investigation as consisting of cough for at least 2 weeks with one or more "pertussis symptoms," namely paroxysmal coughing, post-tussive vomiting, apnea or whoop. When results were analysed using a case definition reflecting more severe disease (cough for 5 or more weeks), vaccine effectiveness improved to 71% for child care centres and 86% for schools. More recently, Bentsi-Enchill et al<sup>12</sup> reported a similar result with their estimate of the effectiveness of the Connaught quadrivalent vaccine using cases from an outbreak of pertussis observed in the Nova Scotia population during 1994. They found that for fully immunized (five doses) children, the effectiveness was 57% (95% confidence interval: 23-77%) when a laboratory-based definition of pertussis infection was used (culture-positive nasopharyngeal aspirate).

In the United States, data are more limited. In the largest prospective study there to date, Onorato et al<sup>6</sup> examined secondary attack rates in 347 pediatric family contacts of index cases with whooping cough. Her group investigated 1797 households for suspected pertussis cases. Of these, 945 households had a family member who met serological, culture or case definition requirements for entry into the study. By following

the 1 - 4 year old household contacts of these patients clinically, as well as with serial nasopharyngeal culture and acute and convalescent serology, the authors demonstrated a vaccine effectiveness (they call it efficacy) of 95% for severe illness (cough for 35 or more days with paroxysms) and 64 % for mild illness (any illness with cough).

Reasons for this relative lack of effectiveness are speculative. Some authors suggest a decrease in efficacy of the vaccines currently in use <sup>19, 30, 31</sup>. This may be due to an as yet unknown mutation of the bacteria which renders it less easily affected than before. Others suggest the vaccine failure-induced accrual of susceptible individuals over time, resulting in an increase of vulnerable persons to a level above the threshold required for sustained transmission <sup>21</sup>. Several authors suggest waning vaccine protection over time so that adolescents and adults who were vaccinated in infancy can act as reservoirs for infection of younger children <sup>2, 22, 31</sup>. It is believed by some that vaccine protection lasts a maximum of 12 years <sup>2</sup>. One group proposed that over reporting of vaccination by parents may be at least partially responsible for the apparent failure rates <sup>6</sup>. This group suggested that parents, aware of the need to vaccinate their children, may be hesitant to report the lack of vaccination to doctors and health department officials. This would lead to an increased pool of seemingly vaccinated but truly unvaccinated children being included in the calculations of vaccine efficacy and a resultant underestimation of that quantity. Finally, most authors believe that an increased awareness by physicians of the disease and its consequences has lead to increases in diagnosis <sup>21, 28, 30</sup>.

### *Whole Cell Vaccine Side Effects*

As a further impediment to pertussis vaccine effectiveness, there has long been widespread public and professional dissatisfaction with its side effects profile<sup>32</sup>. Currently employed whole-cell pertussis vaccines are manufactured from *Bordetella pertussis* which are grown in bulk culture and then harvested. After centrifugation to concentrate the organisms, they are suspended in a buffered saline solution. The bacteria are then killed or partially detoxified by physical or chemical methods producing a mixture of multiple bacterial antigens. This mixture is then combined with diphtheria and tetanus toxoids adsorbed to aluminum to produce the widely used “DTP”(diphtheria, tetanus, pertussis) vaccine<sup>28</sup>. The whole cell vaccine thus contains many different pertussis antigens. Some of these antigens are immunogenic, while others have toxic effects<sup>22</sup>. It is these toxic antigens which are believed responsible for the side effects of pertussis immunization.

Most of the side effects of whole cell pertussis vaccines are mild and associated with only local symptoms. The most common of these include local pain, redness, swelling and induration. Mild systemic reactions are also seen frequently and include low grade fevers, drowsiness, fretfulness, anorexia, and, less commonly, vomiting<sup>33</sup>. Very occasionally, more severe “reactions” can occur. It is these reactions which have generated the most negative publicity and consequently, have been the most damaging. Such reactions include persistent, inconsolable crying (more than 3-4 hours),

high fever ( $\geq 40.5^{\circ}\text{C}$ ), hypotonic-hyporesponsive episodes, convulsions, and encephalopathy<sup>33</sup>. Some authors have even suggested a link between sudden infant death syndrome (SIDS) and pertussis vaccine<sup>34</sup>, though such a link has not been supported in other studies<sup>35, 36</sup>.

Negative publicity about such links and “reactions” in some countries has resulted, at least briefly, in the state-advised cessation of pertussis immunization<sup>2, 38</sup>. This resulted in a loss of effectiveness for the vaccine in those countries and a subsequent surge in the incidence rate of pertussis infection<sup>2, 37</sup>. In North America, while we have continued to use the whole cell vaccine since its introduction approximately 50 years ago<sup>21, 30</sup>, its use has met with increasing opposition. This is compounded by the mass media which continues to promulgate the existence of severe and substantial side effects with ongoing fervour<sup>30</sup>.

However, despite the relatively extreme international response, even the existence of severe neurological reactions to pertussis vaccine continues to be controversial. The earliest reports of such reactions appeared in 1933<sup>38</sup> and have been continuously propagated since. The largest study of such reactions to date has been the National Childhood Encephalopathy Study (NCES) which was conducted in the UK in 1976. It found that children admitted to hospital with a serious acute neurological illness were more likely than control children to have received DTP injection in the previous 7 days than non-affected controls<sup>39-41</sup>. Subsequent follow-up of these children has shown

that they continue to have chronic nervous system dysfunction 10 years later<sup>42</sup>.

Explanations for these effects have been varied but, in addition to a causal relationship, include the possibility that the DTP injection “triggered an acute neurological illness in children with underlying brain or metabolic abnormalities.”<sup>33</sup> It is felt that such children might go on to have chronic central nervous system dysfunction if exposed to other stressful stimuli such as fever or infection<sup>33</sup>. The vaccine may also have caused an acute neurological illness in children for whom a chronic neurological disorder was destined to develop, whether or not the acute illness had developed<sup>33</sup>. The NCES data was not able to reliably discriminate between these possibilities.

In contrast to the NCES data, some studies have not found an increased risk of neurological complications related to DTP immunization<sup>43-47</sup>. In the largest North American investigation of this issue to date, Gale and his colleagues conducted a case-control study in Washington and Oregon<sup>48</sup>. His group found that there was no statistically significant increase in risk of complex febrile seizures, seizures without fever, or acute encephalopathy / encephalitis in children who had received DTP vaccine within 7 days of the onset of their illness. However, they acknowledged that their study had insufficient power to detect a difference in very rare events.

The medical controversy surrounding such severe reactions, accompanied by ongoing public pressure, spurred governments and pharmaceutical companies to work to develop a less reactogenic vaccine for pertussis. It is through this process that the



acellular pertussis vaccine was created<sup>31</sup>. Studies on the efficacy and reactogenicity of these vaccines have dominated the pediatric literature on pertussis for the last ten years.

### *Acellular Pertussis Vaccines*

Acellular pertussis vaccines, rather than being mixtures of numerous pertussis antigens in unknown quantities and proportions, are composed of a number of purified, known pertussis antigens in a predetermined mixture. The actual antigens comprising the mixture vary with the brand of vaccine. All vaccines contain a chemically or biologically detoxified version of pertussis toxin (PT), a protein elaborated by *Bordetella pertussis*<sup>48</sup>. PT is believed by some<sup>50, 51</sup> to be the primary mediator of the clinical disease resulting from pertussis infection. Other investigators do not support this view<sup>48</sup>.

Other vaccine components include filamentous hemagglutinin, pertactin and fimbriae. These molecules are also proteins and are termed adhesins, reflecting their role in the adherence of *B. pertussis* to a variety of cells. It is thought that these adhesins are instrumental in the attachment of *B. pertussis* to the respiratory epithelium, from where the organisms multiply and exert their clinical effects<sup>48</sup>. Paradoxically, they may also be involved in attaching the bacteria to macrophages<sup>52</sup>. Hence, the inclusion of such proteins in a vaccine could potentially prevent “the establishment of infection or make organisms more susceptible to host defences”<sup>48</sup>.

Acellular pertussis vaccines were first tested in Japan where they displayed effectiveness rates similar to, but slightly lower than those observed with whole cell pertussis preparations <sup>53</sup>. The side effects profile, however, was much improved over that seen with the latter <sup>54</sup>. Similar findings have been observed with studies completed in Europe and North America over the last decade <sup>31,32,55,56</sup>. While insufficient numbers of subjects have been tested to ascertain the incidence of rare clinical events such as encephalopathy or SIDS and their potential relationship to the new vaccines, minor and moderate side effects have been significantly reduced. The improvement in the latter has been so great that the American Academy of Pediatrics Committee on Immunization has recently changed its recommendations so that acellular pertussis preparations are now the pertussis vaccine of choice for infants and children in the United States <sup>56</sup>. Canada is expected to adopt similar recommendations soon. The interested reader is referred to Cherry's excellent, comprehensive review of this topic for a more detailed discussion of the history of acellular pertussis vaccines, and the comparative efficacy and reactogenicity results of all of the individual trials to date <sup>54</sup>.

*Implications of Acellular Pertussis Vaccines for the Future*

Despite these promising improvements in side effects profiles, it is notable that none of the trials of acellular pertussis vaccine showed an improvement in clinical efficacy when compared with the standard whole cell pertussis vaccine as currently administered in North America (total of 5 doses)<sup>36</sup>. This means that breakthrough cases continue to be likely and that if eradication is ever to be achieved, a repeat booster dose of vaccine may be required in adolescence or adulthood<sup>2</sup>. It also indicates that while prevention may be optimal, in the absence of a perfect vaccine, and in the face of the evidence above, the practical necessity of providing some effective treatment for the disease remains present.

## **Treatment of Pertussis**

### *Historical Treatments*

The need for an effective treatment for established pertussis illness is not new. As early as the sixteenth century, the *chin cough*, as it was known, was creating treatment problems for the "physicians" of the day. At that time, Gerard, a well-known herbalist, recommended the plant *lysimachia* (Creeping Jenny) which "boiled in wine with a little honie, or meade, prevaieth much against the cough in children called the chinne cough." <sup>57</sup>. The less conventional, tried even more drastic measures to get rid of whooping cough. A tribe in India uses a broth made of the flesh of the bird *Acridotherus tristis* to cure patients of paroxysms. Rathore and Swarup <sup>58</sup> report that patients taking such a concoction could find some relief from coughing within 24 hours of its use and could be rid of the disease within one week. The following passage is extracted from an article by Yates printed in *Nursing Mirror* in 1978 detailing some more of these folk cures for whooping cough:

"Many a whooping child was required to wear around the neck one of his godmother's garters or a lace from her stays. A cure could be effected, too, by carrying the patient, fasting, into three different parishes on a Sunday morning.....the sufferer might be given new milk from a cup made of holly wood, or wear a necklace made of short threaded twigs from an elder grown in a churchyard.....A bramble growing in the ground at both ends was specially prized - the whooping child was passed under and over it nine times on three successive mornings before sunrise, while those present repeated "under the briar and over the briar, I wish to leave the chin-cough here.".....It was customary.... in parts of northern England, to take a bowl of milk, get a ferret to drink half of it and then give the remainder to the patient.....A favourite gipsy remedy was to let a black snail crawl over a saucer of brown sugar and make it slimy. The sugar was then fed to the patient. A muslin bag filled with live spiders and worn night and day around the neck was equally effective. "

More modern physicians have also tried multiple remedies, both conventional and unconventional, to treat afflicted children. Unfortunately though, the development of an effective treatment for the paroxysmal coughing of pertussis patients has been hindered by the lack of a complete understanding of the pathophysiology behind its development. The following sections will review these remedies and the proposed pathophysiological mechanisms behind them in detail.

### *Antibiotics*

Many pathophysiological mechanisms for the cough have been proposed, but to date, none have been clearly proven to be responsible. Perhaps the most logical would seem to be that the infection was directly responsible. Treating the infection with

an effective antibiotic would then presumably eradicate the organism and result in the disappearance of symptoms. Yet, clinical observation shows that this is only part of the answer. A review by Broomhall and Herxheimer<sup>59</sup> points out that as early as 1953, the Medical Research Council trial<sup>60</sup> showed that chloramphenicol and chlortetracycline could shorten the course of the illness and clear the nasopharynx of disease if given during the *catarrhal* phase of the illness, but had little effect on symptoms if given later on. Subsequent investigations have since shown similar results for erythromycin and cotrimoxazole<sup>61</sup>. While on the surface this sounds promising, since the disease is often recognized later in the course, after the paroxysmal phase has started<sup>1</sup>, treatment in the catarrhal phase is somewhat impractical. Additionally, the child must still endure a full month of coughing.

The erythromycin results have recently been supported by several Canadian trials. The first showed that among immunized patients, those treated with erythromycin in the catarrhal phase of their disease had shorter median durations of cough (38 as compared with 57 days) and paroxysms (28 as compared with 44 days)<sup>62</sup>. The second showed that seven days of treatment with erythromycin estolate was as effective for nasopharyngeal eradication of *Bordetella Pertussis* as the standard fourteen day treatment, but the duration of clinical symptoms was not significantly different between the two groups<sup>63</sup>. Hence, antibiotics are clearly not the only answer.

### *Immune Globulin*

In the same way that antibiotics might be expected to work to eradicate coughing, some investigators support the use of immune globulin to treat patients with pertussis. Widely purported to be of great value in the 1930's and 1940's, it subsequently fell out of favour in the 1950's and 60's when repeat studies failed to confirm the initial positive effects <sup>64</sup>. Despite the opinions held on both sides, however, the initial evidence to support or refute the use of gamma globulin was not based on well-designed clinical trials <sup>65</sup>. The first randomised, double-blind, placebo-controlled clinical trial was completed in 1971 <sup>65</sup> and showed no significant group differences in the number of coughs, whoops, vomiting episodes or suctioning required in hospitalized patients with pertussis. A second randomized controlled trial using a higher dose of pertussis hyperimmune globulin was performed in 1991 <sup>64</sup>. This study showed a significant decrease in the number of whoops for the treatment group, but no difference in the number of coughing paroxysms or vomiting episodes. The study also allowed what it called "standard" treatment of pertussis with such medications as erythromycin and salbutamol. This leaves it open to criticism due to the possibility of group contamination from the other treatments. Hence, gamma globulin does not appear to be effective for cough reduction.

### *Sedative-Hypnotics*

Some investigators felt the cough was central in origin, since it seems to persist long after the “active disease” has gone from the respiratory tract. They consequently advocate sedatives such as phenobarbital and diazepam <sup>66</sup>. There have been no clinical trials on this issue to date. Evidence is completely anecdotal, consisting mainly of letters to the editor of various clinical journals describing individual cases or small groups of patients who responded to such treatment <sup>59</sup>. While sedation may be effective for symptom control, it is unclear as to whether this represents an effect on the underlying pathophysiological mechanism or is simply a result of the sedation. Additionally, the side effects of these medications are not insignificant. Most modern physicians would agree that risks versus benefits must be carefully weighed before embarking on such a course of treatment. For this reason, sedative-hypnotics to treat whooping cough have largely fallen out of favour.



### *$\beta_2$ Agonists*

Another potential explanation for the incessant coughing is bronchial hyper-responsiveness following pertussis infection. This stems from animal work in the 1950's which showed that certain strains of mice or rats became hypersensitive to nonspecific stimuli following *B. pertussis* infection<sup>67</sup>. Further support for this theory was claimed by Badr-El-Din and his colleagues who noted an attenuated hyperglycemic response to epinephrine in pertussis patients<sup>68</sup>. These researchers postulated that the mechanism for such airway hyper-responsiveness and pancreatic hyporesponsiveness may have been beta receptor blockade and, therefore, that beta agonists would be a logical treatment. Given current understanding of the pathophysiology of pertussis infection, it seems more likely that the pancreatic hyporesponsiveness to epinephrine was the result of high circulating levels of pertussis toxin, leading to hyperinsulinism in research subjects<sup>2</sup>. The high levels of this counter-regulatory hormone might cause an attenuated hyperglycemic response to epinephrine.

A single clinical trial of salbutamol, a beta receptor agonist, in Egyptian children suggested a potential beneficial effect with an 80% decrease in the number of coughing paroxysms in children treated with nebulized salbutamol<sup>69</sup>. However, design and implementation flaws in this paper make interpretation of the results difficult. Subsequent investigations using *oral* salbutamol, though also limited in their designs, have had conflicting findings. Two studies found no difference in the number or duration

of paroxysmal coughing spells reported by pertussis patients<sup>70,71</sup>, though one of these did report that the number of whoops was decreased in the group treated with salbutamol<sup>70</sup>. One study of 50 patients, which was reported in the form of a letter to the Lancet, did find a difference in the number and duration of both cough paroxysms and whooping between the treated and untreated group<sup>72</sup>. Unfortunately, the authors did not provide any statistical analysis for the data so the significance of the result is unknown. Consequently, the question of the utility of salbutamol in pertussis has still not been effectively answered, though current concepts of pathogenesis do not support a bronchospastic origin for respiratory symptoms.

*Other Treatments*

Other researchers have proposed less conventional treatments. Flights at high altitude have apparently been advocated by some physicians for many years<sup>73-75</sup>. A recent letter to the editor of the *Lancet* detailed one physician-pilot's experience with several patients who reportedly had transient relief from this "treatment"<sup>73</sup>.

Unfortunately, the cough did return when the plane landed. Another pediatrician reports using repeated subcutaneous injections of "woop," a pure pertussis vaccine on a weekly basis for four weeks or until coughing stopped, whichever came first<sup>76</sup>. He reports better results in the partially immunized population, saying that occasionally after just a single injection, the child stops coughing. No figures detailing overall results are provided. The pathophysiological basis for these treatments remains to be elucidated.

### *Steroids*

Of all of the treatments proposed for pertussis, however, perhaps that which has spurred the most discussion has been the use of corticosteroids.

Pathophysiologically, the use of steroids is supported by presently held theories concerning infection and the generation of symptoms. One of these theories has recently been described by Hewlett. The process is believed to begin with the inhalation of *Bordetella pertussis*-containing droplets, aerosolized by the coughing of an affected individual, by a susceptible host. These organisms then attach to the ciliated cells in the nasopharynx by means of various surface proteins known as adhesins. Anchored by these adhesins, the organisms proliferate and spread, eventually extending down to attach to the epithelial cells of the trachea and bronchi. Once established in the tracheobronchial tree, the bacteria are believed to produce a number of cytotoxins including pertussis toxin (PT) and the more recently described tracheal cytotoxin (TCT). These toxins result in paralysis of cilia and the destruction of the tracheobronchial cells. With increasing damage, the host's immune system is activated and inflammatory cells flood the area<sup>48</sup>. The combination of sloughed cells and inflammatory exudate may explain the incessant coughing seen in the disease during the paroxysmal phase. These findings are supported by the fact that microscopic examination of the respiratory tracts of patients with early pertussis shows inflammation of the mucosal lining<sup>1</sup>. Further examination shows the infiltrate to be primarily lymphocytes and polymorphonuclear leukocytes<sup>77</sup>. In the same

way that steroids work to decrease the airway inflammation in conditions such as asthma, through their alteration of lymphocyte DNA synthesis<sup>78</sup>, they could be expected to work in pertussis.

An alternate hypothesis has been proposed by researchers in Japan who have recently documented an increase in substance P, a neuropeptide known to cause coughs in guinea pigs, in patients with pertussis. The elevation in the peptide level resolves with recovery from the paroxysmal phase of the illness<sup>79</sup>. Substance P is elaborated by the sensory nerve terminals of C-fibres found in the airways. While normally protected by the respiratory epithelium, the authors propose that exfoliation of the bronchial epithelial cells during pertussis infection exposes the unmyelinated C-fibres making them more sensitive to stimulation by irritants and increasing production of substance P. If this is the case, then perhaps decreasing airway inflammation with the use of anti-inflammatory medications such as corticosteroids could reduce this exfoliation, thereby reducing substance P and the coughing observed.

Unfortunately, all of the steroid studies have been marked by significant methodological errors, as discussed in the literature review to follow. Additionally, most studies to date have focused on the use of systemic steroids as opposed to the inhaled agents. Considerable unpublished anecdotal evidence exists to support the use of the newer inhaled steroids in this population. For example, a number of staff pediatricians at the Janeway Child Health Centre have found favourable responses in patients treated with

inhaled steroids when compared with patients who are not. More recently, a letter to the editor of *The Pediatric Infectious Diseases Journal* reported on the treatment of 27 pediatric patients with inhaled budesonide<sup>40</sup>. All improved, based on a clinical scoring system, within 72 hours of beginning treatment. This is the first published account of the use of inhaled steroids in pertussis. There were numerous problems with the design of this study. These included the lack of specified inclusion/exclusion criteria, the non-randomized treatment administration, and the absence of a specified outcome measure, among others. When combined with the lack of detailed reporting of this study, such problems make it useful only for hypothesis-generation.

Consequently, the magnitude of the steroid effect clearly needed formal assessment before the question of usefulness could be adequately answered. For this reason, a study was proposed to examine the effectiveness of inhaled steroids in reducing the duration of paroxysmal coughing in patients with pertussis seen at the Janeway Child Health Centre.

## **Review of the Literature on Steroid Use in Pertussis**

Interest in using steroids to treat pertussis began in 1973 with a study by Zoumboulakis, Anagnostakis, Albanis and Matsaniotis <sup>81</sup>. These researchers found a decrease in the number of coughing paroxysms and vomiting episodes, as well as a more rapid recovery, in pertussis patients who were treated with intramuscular hydrocortisone, as compared with untreated controls. Subsequently, there have been only seven other reports which have examined the use of steroids in this disease <sup>69, 78,80,82-85</sup>. These have shown variable results when other steroid medications have been tested. Five studies and a case report upheld the original beneficial effect on coughing <sup>78,80,82-84</sup>, while two other trials were unable to document any significant differences between steroid and control groups. The Badr-El-Din et al. study <sup>69</sup>, however, did find a reduction in vomiting and an improvement in general well-being in the steroid-treated group. Also, both the Roberts et al. study <sup>85</sup> and the Badr-El-Din et al. study <sup>69</sup> showed a reduction in the duration of paroxysmal coughing in the steroid group, but were unable to show statistical significance.

Unfortunately, however, all of these studies were strewn with flaws. First, most of them had an extremely small sample size <sup>69,78,84,85</sup>. Four of them had 10 or fewer patients per study arm <sup>69,78,84,85</sup>. Hence, findings have to be reviewed in that light. Secondly, many had problems with outcome variables. None of the studies clearly defined the primary outcome variable under investigation. While most used the frequency

of paroxysmal coughing episodes as an outcome<sup>69,81,82</sup>, none defined what a paroxysm was. Some studies used multiple outcome variables without designating one as the primary variable, making analysis and interpretation difficult<sup>80-82, 85</sup>. As well, methods of data collection were not given in the majority of papers<sup>69,78,80,82,84,85</sup>. Invalid or unreliable instruments are another source of potential bias in the existing research.

Thirdly, there were problems related to subject selection and inclusion in the studies. Most researchers used a combination of clinical and laboratory data to diagnose pertussis for the purposes of the study<sup>69,78,82</sup>. However, none clearly defined what specific laboratory data were used in the diagnostic decision and only one paper<sup>82</sup> listed the specific clinical inclusion criteria used. Additionally, the majority of investigators did not use any particular duration of coughing at entry into the study as an inclusion criterion<sup>69,78,80,85</sup>. This leads to possible bias through the assignment of patients with later disease to a particular group, since these patients might have been expected to improve more rapidly than those with early disease.

Also of consideration were the problems in subject randomization. While three of the trials claimed to be randomized<sup>78,81,85</sup>, only one gave the procedure used in the "randomization" process<sup>81</sup>, namely, assigning subjects alternately to treatment and control groups. This does not constitute true randomization and must be considered a flaw in the study.

Perhaps the greatest difficulties in interpretation of the above studies are



encountered in the area of data analysis. The most notable problem in this regard is that researchers failed to give the statistical test used in the analysis of the data<sup>69,78,81,85</sup>. This makes interpretation of their work virtually impossible. One study concluded significance without apparently analysing the data<sup>82</sup>. As well, no study provided data to substantiate the assumptions made that the outcome variables measured had a normal distribution. This also limits the usefulness of the data.

Finally, it is also significant to note that no researcher was able to document any ill effects resulting from the use of systemic steroids in patients with pertussis. One group specifically examined this issue as it relates to lymphocyte subpopulations and the possibility of significant immune suppression<sup>78</sup>. They found a decrease in the cytotoxic/suppressor T-cells in the steroid-treated group which was associated with a significant improvement in whooping and no clinical ill-effects when compared with untreated controls.

## **CHAPTER 2**

### **Research Question and Method**

#### **Research Question**

Does the short-term use of inhaled beclomethasone, as delivered by pediatric aerochamber and mask, significantly decrease the duration of paroxysmal coughing in young children with early pertussis, as compared with inhaled placebo?

#### **Research Design**

This study was a double-blind, randomized, placebo-controlled clinical trial.

#### **Sample Size Calculation:**

The number of subjects required to show a significant result if, in fact, one exists is calculated as below. Estimates of the mean duration of paroxysmal coughing are taken from the 1973 paper by Zoumboulakis et al., as previously described<sup>#1</sup>. In that study, mean duration of paroxysmal coughing was 19.3 days after onset of treatment (30 days after the onset of disease), with a standard deviation of 6.5 days. It was arbitrarily decided that to be "clinically significant," a 25% decrease in the number of days to cessation of coughing would be required. The absolute number to which this corresponds,

is calculated from the mean duration of paroxysmal coughing as above (ie.  $0.25 \times 19.3 = 4.825$  days).

Using these two numbers: the standard deviation of the mean duration of paroxysmal coughing and the level of change accepted as clinically significant, as calculated above, the sample size can be calculated from the formula for independent groups. Alpha has been set at 0.05 and beta has been set at 0.1 giving Z values of 1.65 and 1.28 respectively. This gives a sample size of:

$$\begin{aligned}
 & 2 \left[ \frac{(z\alpha + z\beta)SD}{\mu_1 - \mu_2} \right]^2 \\
 &= 2 \left[ \frac{(1.96 + 1.28)6.5}{4.825} \right]^2 \\
 &= 38 \text{ subjects per group} + 20\% \text{ for attrition} \\
 &= 46 \text{ patients per group}
 \end{aligned}$$

**Inclusion / Exclusion Criteria**

Subjects were eligible for inclusion in the study if they had the following characteristics:

1) One of:

a) A clinical history compatible with *Bordetella pertussis* infection. This must have included a history of paroxysmal coughing which may or may not have occurred following a period of catarrhal symptoms. The coughing paroxysms may or may not have been followed by vomiting, apnea, cyanosis, or an audible whoop.

OR

b) A positive culture for *Bordetella pertussis*.

2) Early disease (ie. less than 21 days of paroxysmal coughing).

3) Age 0-7 years.

Patients with the following characteristics were excluded:

1) Refusal to participate.

2) Presently on steroids for other purposes (eg. asthma or rheumatoid arthritis).

3) History of active or quiescent pulmonary tuberculosis.

4) History of untoward reaction to beclomethasone.

### **Subject Recruitment**

It was originally planned that subjects would be identified entirely through referrals from the emergency room, staff pediatricians, pediatric residents and the microbiology laboratory at the Janeway Child Health Centre, St. John's, NF. The Janeway is a 100-bed pediatric hospital serving the child and adolescent population of Newfoundland and Labrador. Its microbiology laboratory receives all samples of nasopharyngeal calcium alginate swabs for isolation of pertussis. In addition to centre-specific recruitment efforts, family and general practitioners were to be canvassed for patients by means of a letter campaign. In consideration of the rates of positive cultures from the microbiology laboratory and the numbers of patients seen presenting to the outpatient department in 1993, it was estimated that an accrual rate of 30 patients per year would be necessary in order to meet the enrollment requirements of the protocol. Given what investigators felt was a relatively benign intervention and the theoretical benefits potentially associated with this treatment, it was expected that such an accrual rate would be possible and, therefore, that the study was feasible.

Unfortunately, recruitment proved to be the major obstacle in implementation of the trial. Review of interim data on reasons for the poor enrollment rates was completed by the primary investigator and members of the supervisory committee at various points during the investigation. These reviews revealed a number of

problem areas. As these were identified, strategies were implemented to try and resolve them.

At the start of the trial, the research protocol was presented to pediatricians and house-staff at the annual Pediatric Research Forum as an upcoming project. Despite this “advance advertising,” accrual was initially hindered most by poor referral rates. In order to improve these, two letters were sent to pediatricians, children’s emergency department physicians and the infection-control nurse at the Janeway Child Health Centre explaining the study and requesting that any patients admitted to the hospital or seen as outpatients, be referred for entry into the study. An example of one of these letters is included as Appendix A. The same letter was sent to pediatric residents training at the Janeway Child Health Centre. Additionally, letters were sent to each of the local general practitioners listed in the local research interest group asking for their cooperation in referring patients from their offices (see Appendix B). As a follow up to this letter, an information dinner on pertussis was used to educate local physicians about the study, and to ask them to refer their patients for enrollment.

In addition to efforts to improve recruitment from physician referrals, lab surveillance was also increased. The research nurse visited the microbiology laboratory every day and recorded the names of patients who had had nasopharyngeal swabs performed on the previous day. All patients for whom swabs for pertussis were collected were considered as being potential study candidates. Attempts were made to contact these

patients by telephone and to recruit them for the trial. A maximum of three telephone calls were made. Where answering machines were present, messages were left but seldom returned. Consequently, many potential subjects remained unreachable.

If contacted, parents of potential subjects were asked a number of questions to determine whether or not the children met inclusion and exclusion criteria. In particular, questions about asthma generated the most discussion as this disorder may be easily confused with pertussis, particularly if the child exhibits symptoms of the cough-variant form of asthma. Consequently, parents of all potential subjects were asked if their children had asthma during the course of the screening interview. If the response was positive, they were asked to compare current symptoms with previous exacerbations of asthma. If symptoms were the same then the potential subject was excluded on the basis that he or she did not meet the clinical case definition and was, therefore, ineligible for inclusion in the study. While many potential subjects were excluded by this method, overall, the increased laboratory surveillance resulted in the most significant increase in potential subjects.

Another reason for low enrollment was the exclusion of subjects who had been coughing too long. The initial inclusion criteria had required that patients be coughing less than 14 days. After the enrollment of the first three patients, this was lengthened to 21 days when it was noticed that several of those subjects screened had been excluded due to protracted cough. This change in the protocol was not expected to

significantly affect the results because of the long duration of coughing in the disease. Despite this change, however, significant numbers of potential subjects still had to be excluded because they exhibited more than 21 days of paroxysmal coughing. In an effort to further address this problem by increasing the referrals of patients with early disease, Public Health Nurses (PHN's) were contacted and asked to refer any patients with *clinical* pertussis detected during their well-baby clinics or home visits. The fact that laboratory diagnosis was not required for admission into the study made this possible.

In addition to the difficulties in referral, an unexpected reason for poor recruitment was parental refusal. Parents were consistently alarmed by the fact that the anti-inflammatory medication in the treatment arm of the study was a "steroid." The widespread discussion of anabolic steroids in the lay press, as well as an increasing public awareness of the systemic effects of oral corticosteroid preparations, perhaps made many parents wary of starting such a medication. This was particularly true in light of the absence of a guaranteed therapeutic response. This issue was addressed by providing detailed explanations of the lack of systemic side effects with short-term use of inhaled corticosteroids and the differences between glucocorticoids and anabolic steroids. Despite this, however, many parents remained hesitant to treat their children with such a medication.



**Randomization**

Subjects successfully recruited were randomized by blocked, stratified randomization to either treatment or placebo, using a sealed envelope system.

Stratification was based on age; group one consisted of those patients less than one year old and group two consisted of those one year old or older. Blocking was completed in groups of four. Stratification was done because of anticipated differences in disease severity in infants less than one year old. Blocking was done to ensure relative equality of the numbers of subjects randomized to each group, given the relatively low sample size required.

Two sets of envelopes, one set white and one blue, were sequentially numbered and separated into groups of four. Interventions (drug vs. placebo) were assigned to particular envelopes by a disinterested third party using a draw system. This system worked as follows: for each group of four envelopes, one of four pieces of paper was selected from a "hat" containing two papers labelled "A" and two papers labelled "B". The letter of the intervention selected was written on a card which was, in turn, placed inside the envelope and the envelope sealed. Each selected piece of paper was kept to one side until all of the pieces in the "hat" had been drawn, and thus, all of the envelopes in the group of four had been assigned a letter. Papers were then returned to the "hat" and the process was repeated with the next four envelopes until all envelopes had been filled. All envelopes were then given to the pharmacist. At the start of the study the pharmacist

was asked to choose which intervention would be represented by which letter. The letter code was known only to him until the end of the study. Thus, within each group of four, two envelopes specified assignment to the placebo group and two specified assignment to the treatment group, thereby accomplishing effective blocking.

After consenting to participate in the study, subjects were assigned to the treatment option in a particular blue or white envelope based on their age and sequence of enrollment. The appropriate envelope was ordered by an investigator and selected by the pharmacist. Patients' records denoted only the colour and number of the envelope containing the letter of the intervention to which they had been assigned. Based on the letter in the envelope, the pharmacist dispensed the assigned drug or placebo. Due to difficulties in obtaining unlabelled canisters, usual labels were removed from all canisters by the pharmacist and replaced with a standardized typed white label listing the patient's initials, study identification number, and the words "use as directed." The canisters were dispensed in identical unlabelled white delivery systems. After the initial interview and device-use teaching had been done, the medication was given to the parent to administer. In most cases, the initial dose was given by the research nurse in the presence of the parent as a demonstration of proper technique.

**Intervention**

Subjects received one of:

-Beclomethasone (Beclovent ®) 100 mcg (2 puffs of 50mcg/puff preparation)  
three times daily

OR

-Inhaled placebo 2 puffs three times daily

All medications were administered by aerochamber™ and mask. This regimen was prescribed for a total of 30 days.

All subjects in both groups were also started on erythromycin therapy for 14 days if it had not already been prescribed by their primary care physician.

**Compliance**

Compliance with the treatment regimen was assessed by weighing canisters before and after treatment had ended. The change in weight for each patient's canister was compared with expected changes derived from two test canisters used in the pharmacy. Based on this, an estimate of compliance was reached for each patient.

**Outcome Measures**

The primary outcome measure for this study was the duration of paroxysmal coughing episodes after treatment was begun.

All of the following were considered secondary outcome measures:

- change in daily cough bout frequency before and after treatment
- complications of pertussis including seizures, pneumonia, and encephalitis (chest X-ray completion and findings were recorded from the chart in an effort to document pneumonias more clearly)
- complications of treatment including facial rash, voice changes, and oral candidiasis
- need for hospitalization and cumulative days in hospital
- parental perceptions of disease as measured by a questionnaire

A number of baseline characteristics were also recorded to ensure potential confounders could be controlled for in the analysis. These included sex, age, duration of coughing and duration of erythromycin therapy at study entry, the presence of atopic diseases (asthma, allergies or eczema), and whether or not the child attended daycare.

### **Definitions**

- *duration of coughing* - the interval in days from onset of treatment to the point when patient is experiencing no more than one coughing episode daily, as reported by the parent
- *cough bout frequency* - the number of coughing episodes in a defined time period as reported by the parent

### **Means of Measurement**

The primary outcome variable was assessed by means of a diary which was kept by the parent (see Appendix C). Parents were also contacted by phone on days 14, 16, 18, 20, 22, 24, and at exit from the study on day 30 to determine the child's progress and to encourage diary completion. A questionnaire (Appendix D) was administered by phone to the child's parents on these days to assess secondary outcomes. Times for interviews are clustered around expected mean duration of illness as reported in the Zoumboulakis et al. study<sup>81</sup>.

The remaining secondary outcome variables were recorded as follows:

- complications of pertussis were taken from the hospital chart and from the parental questionnaire
- number of days in hospital were taken from the parental questionnaire and confirmed from the patient's chart where applicable
- parental perceptions of disease were obtained from a questionnaire administered to parents at the end of treatment
- the frequency of treatment complications including facial rash and/or oral candidiasis was obtained from parental reports as recorded on the exit questionnaire

## Data Analysis

The primary outcome variable for this study was the duration of paroxysmal coughing. Consequently, null and alternate hypotheses were defined as follows:  $H_0: \mu_1 = \mu_2$  and  $H_a: \mu_1 \neq \mu_2$  where  $\mu_1$  represented the mean duration of coughing for the treatment group and  $\mu_2$  represented the mean duration of coughing for the placebo group. Data were analysed using an unpaired, two-tailed t-test. However, since the primary outcome variable was essentially the time to the development of a particular event, namely, cessation of coughing, survival analysis and the log rank test was an equally appropriate test and was also used in data analysis. A twenty-five per cent change was arbitrarily selected as the level at which a change could be considered clinically significant. Consequently, any conclusions to be made from the data were made in this context.

In addition to the primary outcome variable, a number of non-parametric variables have been defined above. Frequency data were analysed using the Chi-square test where appropriate. The type I error was again set at a level of 0.05. Since this was a randomized study and consequently, by definition, any differences between the treatment and control groups will have occurred by chance, demographic variables were not statistically compared.

The problems of repeated significance testing were acknowledged and it was understood that any statistically significant differences evident among the secondary outcome variables would be useful as pointers for possible future areas of study only.

### **Statistical Support**

The SPSS-X statistical package was used for data analysis.

### **Ethical Considerations**

Attempts were made to protect the rights of the subjects. Parents or legal guardians were given an explanation letter prior to enrollment of their child in the study explaining the purpose of the investigation, expected length of participation, and the fact that they could withdraw their child from the study at any time. Parents were asked to give verbal and written consent for their child to participate and were assured of the confidentiality of information given. A copy of the consent form is attached as Appendix E.

In a further attempt to protect confidentiality, subjects names were not used on the data collection forms or questionnaires. Instead, subjects were identified by a code number. Any forms identifying the subject were kept under lock and key, and were only accessible by the researchers and the research nurse. The pharmacist, who dispensed the study medication, also had a list of all those participating in the trial which was kept in a locked drawer in the pharmacy.

The risks associated with the study were minimal and were essentially limited to the risks associated with short-term inhaled steroid use. These include local reactions resulting from irritation or suppression of local immunity and the small possibility of an untoward reaction to the medication. Systemic effects in short term use are negligible. Parents were informed of these possibilities prior to their child's enrollment. Also, parents were advised to wipe children's faces with a damp cloth after each treatment to avoid the deposition of significant amounts of drug on the child's face, thereby reducing reactions. Those old enough to rinse their mouths with water after treatment were also asked to do so in an effort to reduce the incidence of oral candidiasis as a complication.

Parents or guardians were offered access to the results of the study if they desired, and the researcher was available at all times during the study to answer questions should they have arisen. Attending physicians were informed of their patients' enrollment by means of a letter (see Appendix F).

Finally, the proposal was sent to the Human Investigation Committee at Memorial University of Newfoundland's Faculty of Medicine, as well as the Janeway Child Health Centre for approval. Both committees approved the protocol prior to its implementation. Copies of the approval letters are attached as Appendix G.

## **Budget**

A copy of the budget for this project is included as Appendix H.



## **CHAPTER 3**

### **Problems and Solutions**

Throughout the planning and implementation of this project, a number of problems were encountered. Each was addressed and a specific strategy employed to solve it. In the section that follows, the problems encountered will be outlined and the methods used to attempt to solve them will be detailed. For clarity, these have been grouped as: problems related to the selection of an outcome variable, problems in recruitment, and problems with dropout.

#### **Selecting a Primary Outcome Variable**

The initial, and perhaps most time-consuming problem in the design of this study, was selecting an outcome variable. As in any clinical trial, it was important to choose a variable that would have both clinical relevance and practical application. This meant validly and reliably measuring an important clinical effect which was expressed by virtually all patients. Such an ideal parameter proved to be difficult to define.

#### *The Initial Primary Outcome Variable*

As indicated in the introduction, pertussis is an illness characterized by recurrent bouts of paroxysmal coughing which are sometimes, but not always, followed by a whoop<sup>1</sup>. While most studies on pertussis had measured the total number of coughs, whoops, and vomiting episodes per day, most of these investigations had been conducted

in hospitals where a nurse or other professional caregiver may have been assigned to document each episode of coughing, vomiting or whooping<sup>78,81-83,85</sup>. With the move towards ambulatory pediatric care, most patients with pertussis are now cared for on an outpatient basis<sup>4,86</sup>, making this approach no longer feasible. Since reliability and validity were initially felt by the primary investigator to be more important than practicality, the absolute number of coughs in a 4 hour period was initially selected as the outcome variable of choice. It was thought that this variable was both clinically relevant to the patient and could be measured with relative ease, accuracy, and reliability while the patient was sleeping. This seemed to make it a practical outcome to assess.

### *Defining Cough*

Having chosen an outcome variable, however, the investigators were then faced with the absence of a clear definition for a cough. For example, was a cough a single expiratory burst of sound or was it a series of such bursts? If the former were true, how could these bursts be measured with any accuracy? If the latter were correct, how long between cough series was enough to denote a second episode? The questions appeared to multiply the more the issue was considered.

Physiologically, cough can be defined easily as a forced expiratory manoeuvre, differing from forced expiration by starting with a closed glottis which is opened suddenly after intrathoracic pressure has built up, and terminating with reclosure of the glottis<sup>87</sup>. The clinical definition is much more difficult because the exact moment

that the glottis opens and closes is difficult to determine. Further, if one doesn't have the benefit of looking at the patient, distinguishing a cough from a grunt (an important consideration in the pediatric population!) can be a difficult thing. The literature was equally unhelpful in answering this question. Hence, the investigators settled on a compromise definition which defined cough as *any detectable single, discrete, sudden, tussive, expiratory sound, whether occurring in a group or individually*. A "coughing bout" was then defined as *a temporally related group of coughs without an intervening inspiratory sound* and "cough frequency" as *the number of coughs in a defined time period*.

### *Measurement of Coughs*

Having defined the variables to be studied, the next problem was how to measure them with the maximum degree of reliability and validity. Broomhall and Herxheimer had suggested that studies of treatments for pertussis consider using a sound-triggered recording apparatus for cough counting<sup>99</sup>. We did not have any expertise in this method at our institution or in the local area. In order to resolve the problem, a literature search was undertaken to determine whether other investigators had had any success in using this method in the past. Following a Medline™ search using both OVID® and SliverPlatter® software, a single paper was identified. This publication by Loudon and Romans identified a recording system which could be used for cough-monitoring<sup>88</sup>. It employed a complicated procedure using two tape recorders fed by a

single microphone. The first recorder was modified to "hold" the sound in a three second "delay loop" while the second recorder was activated. After travelling through the delay loop, the sound in the first tape recorder was then recorded onto the second one. "The net effect was as though the second tape recorder had been started three seconds before a cough or similar sound, recorded the sound, and then switched itself off again"<sup>88</sup>. Dr. Loudon went on to use this system for recording cough frequencies in patients with such conditions as pneumonia, pulmonary tuberculosis and chronic obstructive lung disease. In a second paper he states that using this equipment, eight hours of coughing in two patients could be read in 1-20 minutes, making it a very practical as well as valid tool<sup>89</sup>.

While too complex for our study, this work provided a starting point for designing a new instrument to measure cough. Additionally, it allowed us to contact Dr. Loudon who subsequently provided other references and some personal suggestions which eventually proved very helpful. Desirable qualities we identified for the ideal outcome-measuring instrument were that it was to be compact, simple to use, able to record for at least 4 hours without need for intervention, specific for coughs, able to give visual output or recording, sensitive over a wide range of frequencies and intensities and inexpensive. Such an instrument would allow maximal information to be extracted in a minimal amount of time. Constructing such a utopian machine proved to be considerably more difficult.

However, in conjunction with the biomedical department at the Janeway Child Health Centre in St. John's, a device was designed and a pilot study initiated to test

the new instrument. The machine consisted of a regular cassette tape deck equipped with an omnidirectional microphone which was placed next to the child's bed. A "sound sensor," which was built into the circuit, was set to activate the tape recorder in response to any sound between 50 and 1500 Hertz which was picked up by the microphone. Once activated, the machine would continue to record for a total of two minutes and then deactivate. Any new sound was capable of reactivating it to record again. Sensory level, or the intensity of sound required to trigger the machine to record was adjustable using a small button on the front of the instrument. A circuit diagram of the entire setup is included as Appendix I.

### *Sample Size*

With a primary outcome variable and a potential measuring instrument, the next hurdle to overcome was the calculation of a sample size. Since the statistical analysis of the trial results would involve the comparison of the differences between two means, in order to calculate a sample size one needed to know the mean and standard deviation of the 4 hour cough frequency in the population to be studied. As this outcome had not been used previously, no such statistics were available. In order to estimate them, as well as test the measuring instrument, a pilot study was designed.

### *Pilot Study*

A pilot study was designed and implemented after approval by the ethics committees at Memorial University of Newfoundland and the Janeway Child Health Centre. The study recruited inpatients with clinical pertussis and recorded coughs over a 4 hour sampling period. Copies of the entire protocol, the consent form used, and approval letters from both the Human Investigation Committees at Memorial University and the Janeway Child Health Centre are included as Appendix J for more detailed information. The initial attempt met with failure when the tape recorder did not activate with coughs. This was attributed to a malfunction in the circuit. A second attempt was made on the next night. Unfortunately, this also met with variable technical success with the recorder working only part of the time and inconsistently activating with coughs. The high maintenance required for this system, along with its bulkiness, made it impractical for parents to use on their own at home. Consequently, the model was abandoned.

Based on a suggestion by Dr. Loudon (personal communication, March 1994) a commercial solution to these problems was found in a hand-held dictaphone. A Radio Shack™ voice-activated dictaphone was purchased and used in monitoring a single patient on two consecutive nights. This machine circumvented not only the technical difficulties experienced with the "homemade" model, but was also compact enough to fit into a shirt pocket. This made it the ideal size for parents to carry home and use. Additionally, setup was very easy with the press of a single button required for activation.

Using the Radio Shack™ model, a single patient had coughs recorded for two consecutive nights. The machine appeared to work well with activation occurring consistently in response to coughing episodes. Unfortunately, however, it also activated with even quiet extraneous noises in the environment. This made interpretation of the tape exceedingly time consuming, with requirements of up to three hours of review time for each night of study. In an investigation which planned thirty nights of observation in each of 64 patients, such a time requirement virtually precluded its use entirely. Additionally, the machine did not provide enough sound resolution to allow clear distinction between different noises such as grunting and coughing. This would have serious implications for the reliability of the outcomes obtained by this method. Because of these difficulties, this measuring device, and eventually, this outcome measure, were abandoned.

#### *Selecting Another Primary Outcome Variable*

Given the difficulties experienced, as outlined above, measured cough frequency was abandoned as a potential outcome measure and the investigators returned to parental reports of cough frequency as the most practical alternative. Data collection sheets were subsequently designed which asked the parents to tally the number of coughs the child had each day. In cases where a child was attending school, the parent was asked to give the cough-record (Appendix A) to the teacher to keep during the day. The problems with parental recall and supervision intrinsic to such an outcome were

acknowledged. However, given that the treatments were to be randomized, it was felt that these influences would most likely be distributed evenly across both groups and that their impact on the final results would thus be minimized.

## **Recruitment**

Having decided on a new primary outcome variable and a means of measuring it, it was possible to move on to the implementation of the actual investigation. The most significant problem experienced during this phase, and the most important in relation to the overall results, was the difficulty experienced in recruiting patients for the study. Of the 560 potential subjects that were contacted, only 23 patients enrolled in the study and of these, only 18 stayed in the study long enough to provide usable data. There were a number of reasons for this. As each was identified, a strategy was put in place to try and minimize its effect. These strategies have been previously listed in the methods section. It is the details of their implementation and their relative effectiveness that is described here.

Initially, recruitment was hindered by poor referral rates. In order to improve these, two letters were sent to pediatricians and children's emergency department physicians explaining the study and requesting that any patients admitted to the hospital or seen as outpatients, be referred for entry into the study. A similar letter was sent to pediatric residents training at the Janeway Child Health Centre. Additionally, letters were sent to each of the local general practitioners listed in the local research interest group



asking for their cooperation in referring patients from their offices. As a follow up to this letter, an information dinner on pertussis was used to educate local physicians about the study, and to ask them to refer their patients for enrollment.

While letters requesting referrals resulted in minimal improvement in recruitment from pediatric resident referrals, referrals from pediatricians, emergency room physicians and general pediatricians remained low. Additionally, the information dinner had the opposite effect from that desired in that some physicians began putting their pertussis patients on inhaled steroids without enrolling them in the trial. This may explain the high proportion of patients with positive pertussis swabs who had to be excluded from the study because they were already on steroids. The particular physicians concerned were telephoned and asked to avoid this practice if possible. While this did improve the situation, a number of potential subjects were lost.

In addition to efforts to improve recruitment from physician referrals, lab surveillance was also increased. The research nurse visited the microbiology laboratory every day and recorded the names of patients who had nasopharyngeal swabs collected on the previous day. All of these patients were considered potential study candidates. Attempts were made to contact these patients and recruit them for the trial. This resulted in an increase in potential subjects.

Another reason for low enrollment was the exclusion of subjects with more than 21 days of paroxysmal coughing. In an effort to increase the referrals of patients with early disease, Public Health Nurses (PHN's) were contacted and asked to

refer any patients with *clinical* pertussis detected during their well-baby clinics or home visits. The fact that laboratory diagnosis was not required for admission into the study made this possible. Unfortunately, PHN subject identification did not improve the enrollment rate significantly.

In addition to the difficulties in referral, an unexpected reason for poor recruitment was parental refusal. Parents were consistently alarmed by the fact that the anti-inflammatory medication in the treatment arm of the study was a "steroid." The widespread discussion of anabolic steroids in the lay press, as well as an increasing public awareness of the systemic effects of oral corticosteroid preparations, perhaps made many parents wary of starting such a medication. This was particularly true in light of the absence of a guaranteed therapeutic response. This issue was addressed by providing detailed explanations of the lack of systemic side effects with short-term use of inhaled corticosteroids and the differences between glucocorticoids and anabolic steroids. Despite this, however, many parents remained hesitant to treat their children with such a medication. Similarly, the idea of a placebo discouraged some parents from having their child randomized.

## **Drop Out**

The final problem experienced was that of drop-out. While 23 patients were initially recruited for the study, only 18 provided useable data. Reasons for dropout will be detailed in the results chapter and will not be reiterated. In order to make maximal use of all available data, when a parent indicated that he or she wanted to remove a child from the study, contact was made with him or her by the research nurse. Parents were asked to return their children's puffers and cough diaries which could have been included in a survival analysis. Unfortunately, none of the parents whose children did not complete the study agreed to do so. This occurred despite repeated calls from the research nurse, as well as offers to pick up puffers and diaries from the subjects' homes.

In these ways, problems encountered by the trial were addressed and the most reasonable solutions which circumstances allowed were proposed. In some cases, these solutions proved acceptable and in others, the situation remained suboptimal. Despite the persistence of such problems, however, a number of children were successfully enrolled in the trial and data was collected from them. The next chapter describes the group of subjects enrolled and details the data they provided.

## **CHAPTER 4**

### **Results**

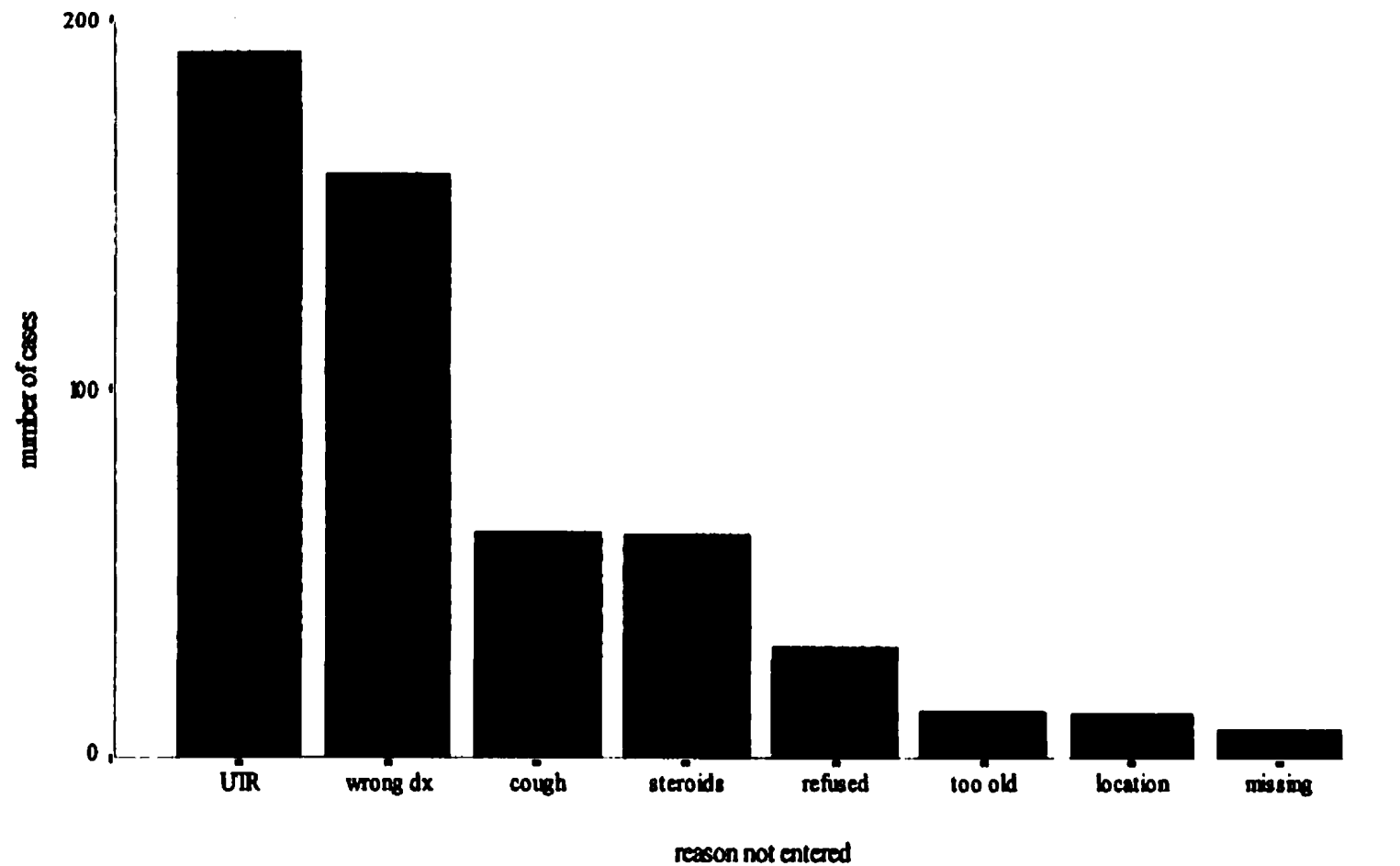
#### **Subjects**

This study was conducted in two periods from January 1, 1995 to April 30, 1995 and from September 1, 1995 to March 28, 1996. These periods were chosen in an attempt to maximize use of available funding through employment of a research nurse only during those periods when the incidence of pertussis was high. Despite the reported lack of seasonal variation by some investigators<sup>1</sup>, the Janeway microbiology records showed that the majority of cases in the local area occurred during the fall and winter months of each year (James Fleming, unpublished data). During the interval of study, 560 referrals, representing 539 patients, were made to study investigators (21 subjects had several swabs done for pertussis during the course of the study period and so were referred twice). Of these referrals, 369 were successfully contacted. The others could not be reached by telephone. Of those contacted, the commonest reason for exclusion was the failure of referred patients to meet the case definition of pertussis. One-hundred-and-fifty-nine referred subjects (28.4%) were excluded for this reason. Sixty-two referrals (11.1%) had been coughing too long to qualify for study entry. Another 61 referrals (10.9%) were excluded because they were already on inhaled steroids. Parents of 31 referrals (5.5%) refused entry of their children into the trial. Thirteen referred subjects (2.3%) were older than 7 years and therefore did not meet inclusion criteria. Parents of

twelve referred children (2.1%) reported living too far from the study centre to enter the trial. Information was not recorded on the reason for exclusion of 8 referrals, comprising 1.4% of the total. These numbers are summarized in table 4.1 and depicted graphically in figure 4.1. The remaining 23 subjects (4.2%) were entered in the trial.

Table 4.1 Reasons For Exclusion Of Referrals Not Entered In Trial

<b>Reason for Exclusion</b>	<b>Frequency</b>	<b>Percentage of All Attempts</b>
unable to reach	191	34.1
failure to meet case definition	159	28.4
coughing too long	62	11.1
on steroids	61	10.9
refused	31	5.5
age > 7 years	13	2.3
location out of town	12	2.1
information not recorded	8	1.4
<b>Total</b>	<b>537</b>	<b>95.8</b>



**Figure 4.1 Reasons for Exclusion of Subjects Not Entered in Trial**

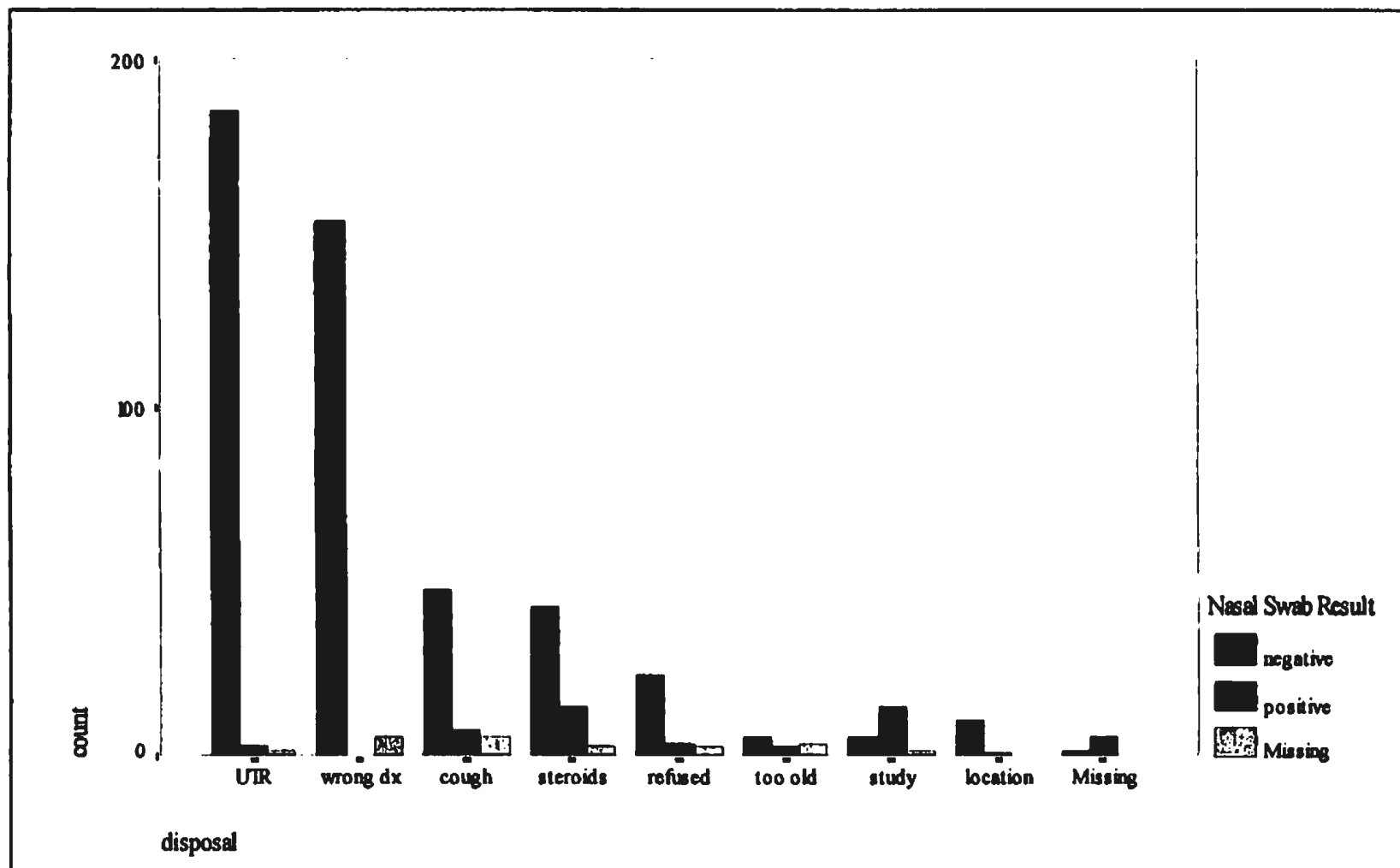
Legend: UTR= unable to reach, wrong dx = did not meet case definition, cough = coughing too long, steroids = already on steroids, refused = refused entry, too old = older than 8 years, location = lived too far from study centre, missing = reason not recorded

The total number of swabs done by the Janeway microbiology lab during the period of study is unknown, as no record of that information is kept. However, the total number of positive results reported to the Department of Health during the study period was 94 (James Fleming, unpublished data). Of these, attempts were made to contact 55. Those with positive swabs who were not contacted included those who were known to be from out of town, those whose age appeared on the requisition and who were older than 7 years, and those who were missed before enhancement of the laboratory surveillance process. The swab results of all potential subjects referred to the trial, along with their disposal, are recorded numerically in table 4.2 and depicted graphically in figure 4.2. Information on swab results was not available for 26 cases and information on reason for exclusion was not available in 8 cases, thus accounting for the total number of patients referred.



Table 4.2 Outcome Of Referrals According to Swab Results

Outcome of Referrals	Swab Results		
	Negative	Positive	Missing
unable to reach	186	3	2
wrong diagnosis	153	0	6
coughing too long	48	8	6
on steroids	43	15	3
refused	24	4	3
location out of town	11	1	0
age > 7 years	6	3	4
entered in study	6	15	2
missing	2	6	0
<b>Totals</b>	<b>479</b>	<b>55</b>	<b>26</b>



**Figure 4.2 Disposal of Referred Patients**

Legend: UTR= unable to reach, wrong dx = did not meet case definition, cough = coughing too long, steroids = already on steroids, refused = refused entry, too old = older than 8 years, study= entered in study, location = lived too far from study centre, missing = disposal not recorded

### **Referral Sources**

Examining the referral source for those in each group shows that 7 subjects in the beclomethasone group were referred by the laboratory with the other 2 subjects referred by a resident and a general practitioner. In the placebo group, 3 subjects were identified through the emergency department, 3 by the laboratory and 1 each from a resident, a pediatrician and a general practitioner. No patients in the beclomethasone group were referred by pediatricians or the emergency department. The source of referral for all patients in both groups is shown in table 4.3.

Table 4.3 Referral Sources

<b>Referral Source</b>	<b>Placebo</b>	<b>Beclomethasone</b>
laboratory	3	7
emergency	3	0
pediatrician	1	0
resident	1	1
general practitioner	1	1

Of patients entered in the study, five withdrew before the end of treatment and before any useable data could be collected. Two patients exited before completion of treatment because the nasal swab subsequently came back negative and parents were unwilling to continue with the medication. Another patient failed to return the cough diary, making estimation of the time to disappearance of cough impossible. A fourth patient exited 2 days following initiation of treatment because of a perceived worsening of cough on the study medication. One patient was withdrawn by the parents after an initial period of perceived benefit, because the child appeared to the parents to become worse and the mother was concerned about the effects of steroids. All patients exiting failed to return the cough diary, making calculations impossible. Of patients who dropped out after randomization, two had been assigned to receive placebo and three had been assigned to receive beclomethasone.

### **Baseline Characteristics**

Of those patients completing the trial, 9 received beclomethasone and 9 received placebo. Comparison of group characteristics at baseline is provided as table 4.4.

Table 4.4 Baseline Group Characteristics

<b>Characteristic</b>	<b>Placebo</b>	<b>Beclomethasone</b>
age in months mean (range)	32.6 (4-95)	44.5 (2-90)
days coughing at entry mean (range)	13.1 (3-21)	14.9 (8-21)
days of erythromycin mean (range)	3.8 (0-8)	5.1 (0-14)
sex	male - 4 female - 5	male - 5 female - 4
asthma (no. of patients)	1	0
allergies (no. of patients)	1	0
eczema (no. of patients)	4	3
daycare attendance (no. of patients)	2	3

As shown in table 4.4, groups were very similar in most characteristics with the exception of age, the beclomethasone group being slightly older overall than the placebo group. Only 4 patients (22%) were less than 12 months old at entry into the trial. The overall average duration of coughing at entry into the study was 14 days, with means for the respective treatment groups shown in the table. Similarly, the overall mean duration of erythromycin therapy at study entry was 4.4 days, with little difference seen between the two study groups. Approximately 28% of patients entered in the trial had been treated for their illness with antibiotics other than erythromycin. Only one subject had not been treated with any antibiotics at study entry. Another 28% of subjects had also been treated with medication other than antibiotics. Of this latter group, two patients were on oral orciprenaline (Alupent®), one patient was taking an over-the-counter cough preparation containing dextromethorphan, one patient was taking acetaminophen for perceived teething-related pain and one patient was on sodium sulamyd 10% eye drops for purulent conjunctivitis. The distribution of these patients between the two groups was similar. Nearly half of recruited subjects reported some evidence of atopic disease with 8 subjects reporting at least one of asthma, allergies or eczema in the past. The relative distribution of subjects with each of these problems is also presented in table 4.4.

### **Baseline Symptoms and Laboratory Findings**

Groups were assessed at the time of entry into the trial to determine whether baseline differences in symptoms or laboratory findings existed. All were coughing at entry into the study since this was an inclusion criterion. Further, 16 subjects exhibited at least one of the relatively “pertussis-specific” symptoms of vomiting after coughing, whooping, apneas, or cyanosis. Overall, 72% of subjects had vomiting during the course of their illness, 72 % exhibited whooping, 17% had apneas and 17% had parentally reported cyanotic spells. Interestingly, parents reported fever in one third of subjects recruited for the trial. The distribution of symptoms at baseline between the two groups are provided as table 4.5. The mean number of coughs per day (with 95% confidence interval (CI)) at initiation of treatment in the placebo group was 11.8 (6.6, 17.0) and 22.3 (6.8, 37.9) in the group treated with beclomethasone.



Table 4.5 Baseline Symptom Frequencies

Symptom	Placebo Group number of patients (%)	Beclomethasone Group number of patients (%)
Vomiting	7 (39)	6 (33)
Whooping	6 (33)	7 (39)
Apneas	1 (6)	2 (11)
Cyanosis	2 (11)	1 (6)
Fever	5 (28)	1 (6)

Pneumonia was reported in only one subject at the beginning of the study with chest X-rays performed in 7 (38%) subjects. Two subjects had chest X-rays reported as showing peribronchial thickening without evidence of atelectasis or pneumonia. One was being treated with placebo and one with beclomethasone. The subject who was treated with placebo had a positive pertussis swab. The beclomethasone-treated subject subsequently grew adenovirus from the nasopharyngeal swab. The rest of the X-rays were reported as normal.

White blood cell counts were available in only 3 subjects in whom they were not elevated with the average being 12.4 in the placebo group. The single subject in the beclomethasone group who had a WBC count done had a count of 13.4. Lymphocyte percentages were mildly elevated with the average percentage being 0.65 in the placebo group. The subject treated with beclomethasone had a lymphocyte percentage of 0.66.

### **Follow-up Calls**

Prior to completion of the study, six follow-up telephone calls were made. The primary purpose of these, in addition to encouraging parents to continue participation, was to assess both progression and complications of the disease, and potential side effects of the medications. At the initial follow-up call made at day 14 after entry into the study, only 1 child had stopped coughing. This subject was receiving placebo. One subject in the beclomethasone group was experiencing apneas and one subject in the placebo group was experiencing fever. Two subjects, one in each group,

were still experiencing vomiting episodes and one subject in the beclomethasone group was still having whoops. A single parent reported pneumonia in a child treated with placebo. No parent reported seizures. Three subjects (2 from the placebo group and 1 from the beclomethasone group) had experienced other complications which had been attributed to whooping cough. One subject in the placebo group complained of sore ears and throat which was treated by the general practitioner with amoxicillin. This otitis persisted throughout the duration of the study and eventually resulted in the subject being treated with an antihistamine and an erythromycin / sulfasoxizole mixture by the general practitioner. A second subject in the placebo group complained of upper respiratory tract infection but was not treated with any new medications. The subject in the beclomethasone group complained of "the flu" which was also treated with amoxicillin. No subject had experienced thrush, noticeable change in voice or facial rash at the time of the first follow-up call. A single subject in the placebo group did report development of diarrhea which had been attributed to the study medication, but which was likely due to the erythromycin.

A second follow-up call was made on day 16. At this time no subject was experiencing apneas, blue spells, fever, vomiting or whoop. Again, however, all but one subject continued to cough. No new subjects had developed pneumonia or experienced seizures. One subject who had been randomized to the placebo group had developed thrush which was being treated with mycostatin, but no one reported any change in voice or facial rash. A second subject in this group was experiencing mild nausea with

occasional vomiting not related to cough. No other potential drug effects were noted by parents.

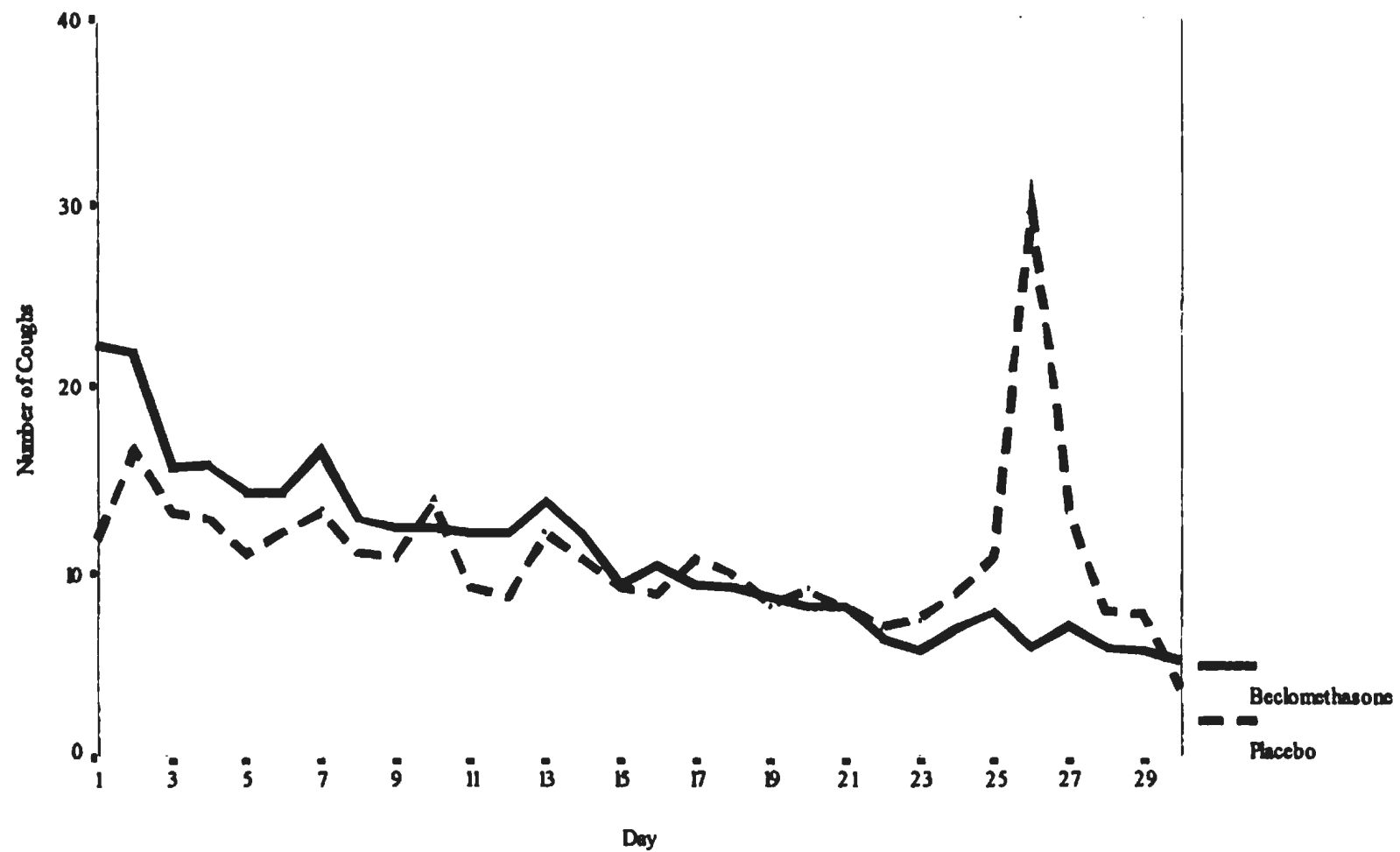
A third follow-up call was made on day 18. At this point, 4 subjects had stopped coughing (2 from each group) while other symptoms remained unchanged. No subject reported any new complications of their disease and there were no new instances of thrush, change in voice, facial rash or other symptoms potentially attributable to the medication.

At the time of the fourth follow-up call on day 20, one of the subjects in the placebo group who had stopped coughing, had restarted. Otherwise, the distribution of pertussis symptoms was unchanged. No new complications of the disease or treatment were reported.

The fifth follow-up call on day 22 saw a switch from the previous in that one of the subjects in the beclomethasone group had restarted coughing having previously stopped. Again, other symptoms were unchanged. The sixth and final call on day 24 was similar in that again, no new symptoms or complications had been reported. At that time only 5 patients had stopped coughing completely. Three were from the placebo group while 2 were from the beclomethasone group.

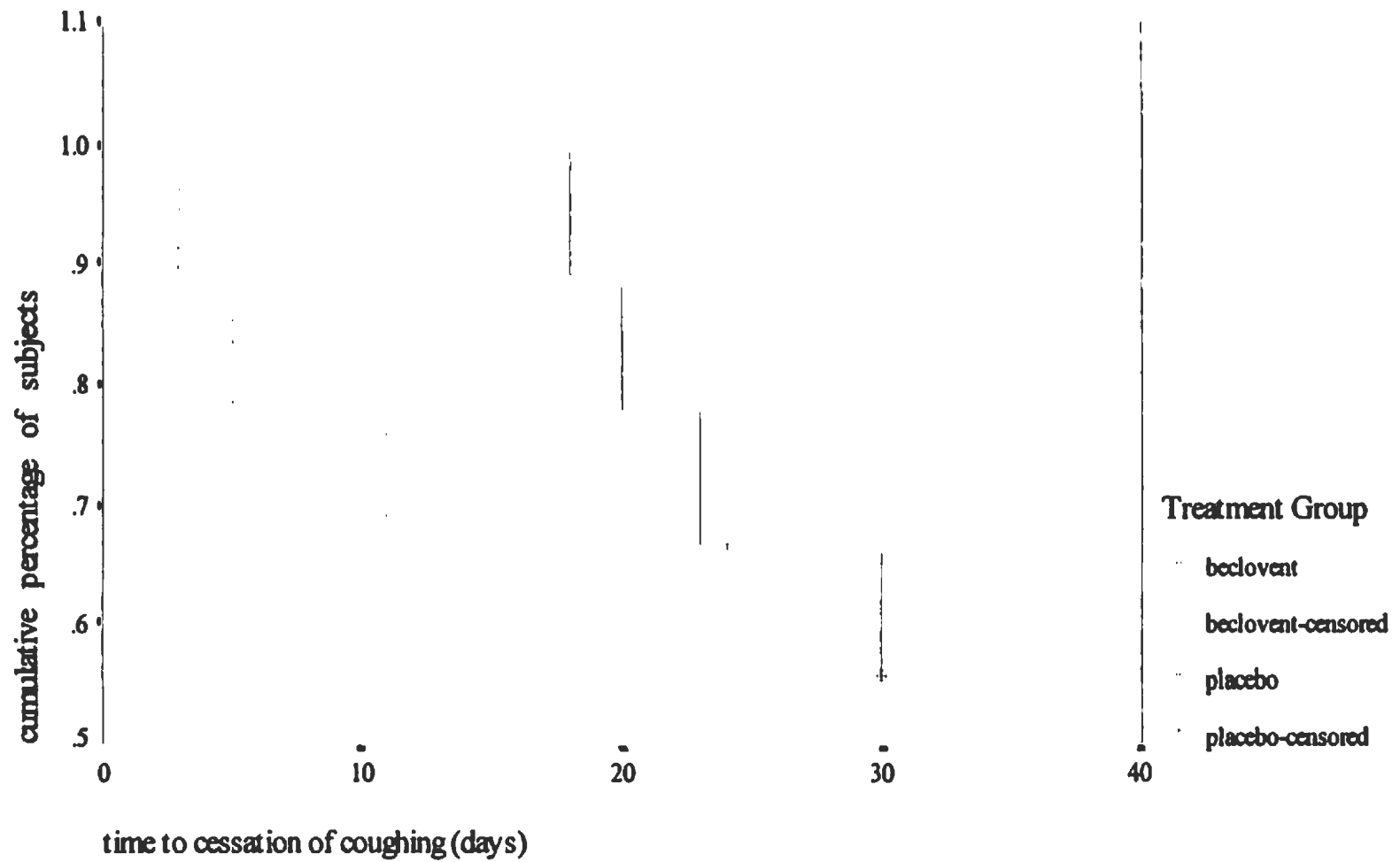
### **Cough Duration**

The primary outcome variable was the time to cessation of coughing. This was assessed from patient diaries kept by the parents and other caregivers for the subjects in the study. A plot of the mean number of coughs for each day of the study for both groups is provided as figure 4.3. The sudden rise in the number of coughs in the placebo group on day 26 is due to one subject who coughed 224 times on that day. This subject had a negative pertussis swab and subsequently grew adenovirus. With this outlier removed, the mean is 5.7.



**Figure 4.3 Mean Number of Coughs per Day for Each Treatment Group**

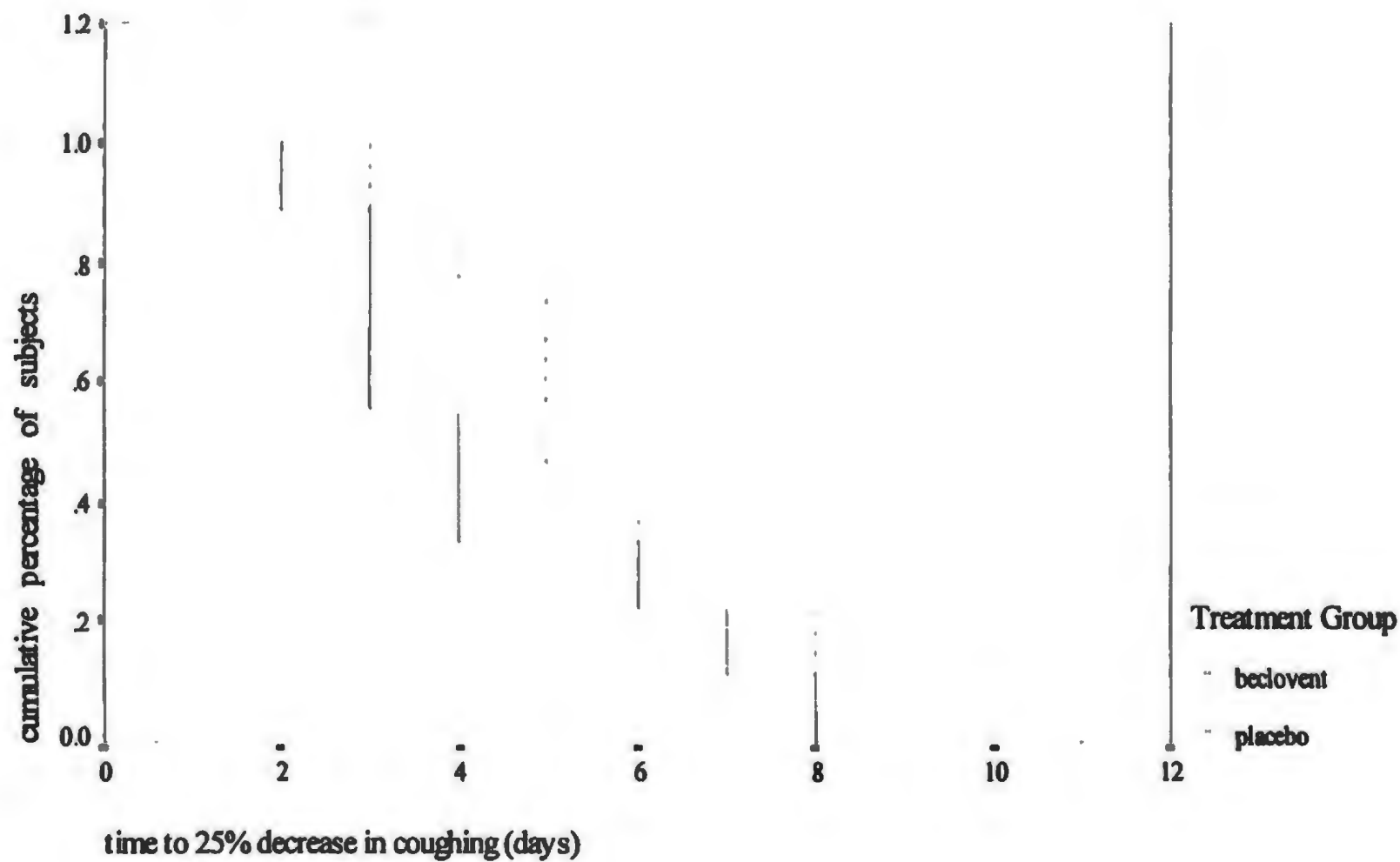
In the beclomethasone group the mean time to cough cessation was 26.8 days while the placebo group had a mean value of 21.4 days. Student's t-test for the difference between these two means gave a p-value of 0.2 with a 95% confidence interval for the difference of (- 14.313, 3.646 ) showing that the result was not significant at the  $p \leq 0.05$  level. This variable was also assessed with survival analysis using the Kaplan-Meier method. Results of that analysis are shown graphically in figure 4.4. From the curves it appeared as though there was a trend towards better performance in the placebo group. Analysis of the curves using the log rank test, however, confirms the results of the t-test and shows no significant difference between groups at the  $\alpha = 0.05$  level ( $p = 0.8$ ).



**Figure 4.4 Time to Cessation of Coughing**

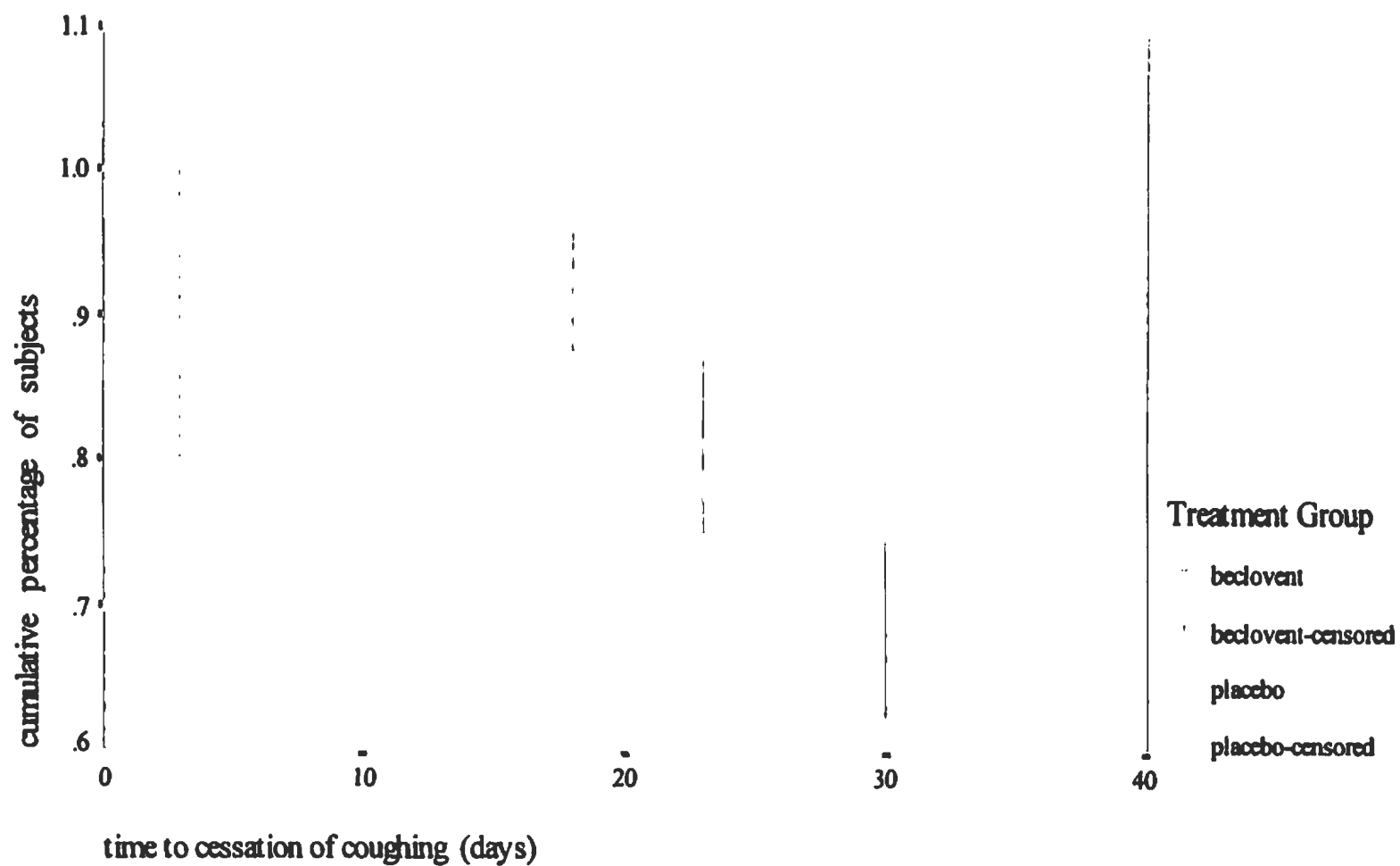


Since the beclomethasone-treated group started with a greater number of coughs per day, the time it took for members of each group to attain a 25% decrease in number of coughs was also assessed in an effort to minimize the inequality. The mean time to achieve this reduction in coughing for the placebo group was 5.9 days and for the beclomethasone group was 4.4 days. Again, Student's t-test failed to show a significant difference between the groups ( $p = 0.19$ ). This is again shown graphically as a Kaplan-Meier curve in figure 4.5. The log rank test confirms the absence of a significant difference between the two curves ( $p = 0.23$ ).



**Figure 4.5 Time to 25% Decrease in Coughing**

Due to the use of a clinical case definition for pertussis, the possibility exists that some subjects without true pertussis infection were included in the trial. To negate the effects of this possibility on the study conclusions, data on just those subjects with positive pertussis swabs were re-analysed with the others removed. The adjusted mean number of days to cessation of coughing was 27.6 for the treatment group and 24.6 for the placebo group. Results of Student's t-test ( $p = 0.61$ ) and survival analysis (log rank test -  $p = 0.61$ ) confirmed the earlier findings that showed no difference between the groups. Graphic depiction of this is included as figure 4.6.



**Figure 4.6 Time to Cessation of Coughing in Subjects With Positive Pertussis Swabs**

## **Compliance**

Compliance was assessed by weighing canisters before and after completion of therapy. Expected weight change was based on a test use of both a beclomethasone and placebo canister. The actual change in weight was divided by the expected change in weight to give an estimate of compliance. In all, 5 subjects who completed the study failed to return their canisters. Using the method described above on data from those who did return their medications gave a mean overall compliance rate of 84%. Breaking it down by groups shows an average compliance rate (95% CI) of 86.1% (66%, 106%) in the placebo group and 81.8% (61%, 102%) in the beclomethasone group. However, of the 5 subjects who did not return their inhalers, 4 were from the beclomethasone group and 1 was from the placebo group. Multiple telephone calls were made to parents of subjects for whom inhalers had not been returned, asking them to return the devices. In some cases, offers were made to pick up the inhalers from the subjects' homes. No inhalers were retrieved in this manner.

## **Disease Impact and Severity**

Parents were all interviewed at exit from the study to determine their opinion of the disease process and its impact on their families. All were asked to rate the disease severity on a five point Likert scale ranging from "mild (like a cold)" to "severe (life-threatening)." They were also asked to report whether the disease had resulted in lack of sleep for the child or themselves. The economic impact of the disease was

assessed by asking whether any of the primary caregivers had been required to take time off work because of the disease. Results are provided in tables 4.6 and 4.7 and showed that most parents in both groups considered whooping cough to be a moderate to moderate-severe disease. Minor group differences were not statistically significantly different. Virtually all parents reported that both they and their children had lost sleep due to the illness and minimal differences between groups were not statistically significant. Few parents reported lost work time as a result of the illness. All those who did lose work time due to the illness were from the beclomethasone group. Results were not statistically significantly different using the Chi Square test.

Table 4.6 Impact of Disease Questionnaire Results

Quality Assessed	Placebo n (%)	Beclomethasone n (%)	Total n (%)
sleep loss (child)	8 (44)	9 (50)	17 (94)
sleep loss (parent)	6 (38)	9 (56)	15 (83)
time off work	0	3 (17)	3 (17)

Table 4.7 Disease Severity as Rated by Parents

Disease Severity	Placebo n (%)	Beclomethasone n (%)	Total* n (%)
mild (like a cold)	0	1 (6)	1 (6)
mild-moderate	0	1 (6)	1 (6)
moderate	3 (17)	4 (22)	7 (39)
moderate-severe	6 (33)	3 (17)	9 (50)
severe (life threatening)	0	0	0

\* Total adds to more than 100% because of rounding

## CHAPTER 5

### Discussion

#### **Recruitment Efforts**

The results of this study are primarily limited by the low numbers of subjects recruited for entry. The reasons for the poor accrual rate are varied but problems may be considered in three groups. These include problems stemming from the trial design, problems resulting from the disease under study, and problems related to the population itself.

#### *Design Problems*

From the point of view of trial design, it became apparent very early that estimates of the numbers of subjects who could be enrolled each month were high. Such overestimation is not uncommon in clinical trials<sup>90,91</sup>. In our case, the problem may stem from the fact that pertussis is a disease for which epidemics are not infrequently reported<sup>2</sup>. The period which was used to estimate the numbers of subjects available for study included one such epidemic year<sup>13</sup>. This epidemic had ended by the time approval from the various ethics committees and granting agencies had been received and the project could be implemented. As a result, fewer children contracted the disease than had been anticipated, and therefore fewer children were available for enrollment in the study.



Another design-related reason for our failure to achieve the desired numbers of subjects was the reliance on other practitioners to make referrals of appropriate candidates for study entry. This recruitment strategy has been consistently inadequate to achieve recruitment goals in large multicentered adult trials of various medications and treatment options<sup>90</sup>. As early as 1983, the Coronary Primary Prevention Trial was plagued by similar problems when only 25% of the required sample size had been enrolled by the midpoint of the recruitment period as a result of relying solely on physician referrals<sup>92</sup>. In that study, the expansion of recruitment efforts to include workplace screening of potentially eligible adults, mass media campaigns, blood bank donor screenings, community screenings and mass mailings improved the accrual rate four-fold. Similarly, a study on diabetes care for older adults<sup>93</sup> reported that only 11% of 418 enquiries from potential subjects were generated by physician referral, with only 6% of the 103 subjects entered in the trial deriving from these referrals. This contrasted with 84% of enquiries and 87% of enrollments generated by referrals from combined community-directed recruitment efforts. Further, a study on the most effective strategy to use to recruit subjects for a study on asthma found that waiting for referrals from other practitioners resulted in recruitment of only 13% of the total subjects entered into the trial when compared with 87% recruited using the alternate methods of actively screening charts and telephoning potentially eligible candidates<sup>94</sup>. These findings were again confirmed by those of the trial of hypertension prevention. The investigators in this group found that the combination of “referrals from medical and dental offices, friends, or

other sources and attempts to recruit from lists of participants from previous research studies yielded only 4% of the randomized group.”<sup>95</sup>

While these authors have emphasized the dangers of relying on other practitioners to provide referrals of subjects for entry into clinical trials, in defence of the strategy we employed, the nature of pertussis infection and the disease it causes mean that options for recruitment in this situation were rather limited. This is particularly true in the setting of the Newfoundland health care system. In this system, pediatricians are not providers of primary health care and, therefore, are not usually the “front line” members of the health care team. When studying a disease like whooping cough, which presents acutely and which may masquerade as a number of other simpler problems, reliance on front line practitioners is necessary. Complicating matters further was the fact that, since recruiting problems had not been anticipated, there was no budget to allow for community advertising, the preparation of posters or the use of other mass media methods to inform the general public and general practitioners about the opportunity for study enrollment. Furthermore, given the current health care system, as outlined above, such advertising may have been seen as an attempt to lure patients and the economic benefits they bring, away from general practitioners. The professional ethics of such a strategy are, therefore, worthy of consideration. Hence, the potential backlash stemming from this situation may have precluded such a recruitment strategy, even if funding had been available.

Other problems with the study design which contributed to the lack of enrollment included the lack of adequate telephone follow-up for contacts. A maximum of three telephone calls were made. Where answering machines were present, messages were left but seldom returned. Extending the number of calls to nine and distributing them more evenly throughout the week may have resulted in improved recruitment rates. Koepsell and his colleagues at the University of Washington conducted a randomized trial of leaving messages on telephone answering machines in order to recruit controls for a study on Lou Gehrig's disease<sup>96</sup>. They used random-digit-dialling to find telephone numbers and called each number up to nine times. These calls were distributed evenly between weekdays during the day, weekday evenings, and weekends. They were successful in reaching 62% of numbers tried when no message was left, but reached 85% of numbers when a message was left. Our own lack of persistence in this area was primarily a reflection of the limited budget with which we were operating, rather than a true design flaw.

Paradoxically, another of the design-related "flaws" which may have contributed to our low recruitment was the choice of a randomized placebo-controlled trial design. The use of a "medicinal placebo" may have enhanced recruitment by making it seem as though subjects were receiving "treatment" in both arms of the trial. Possibilities for such a study include a test of bronchodilators alone in comparison with bronchodilators and beclomethasone; or a comparison of an oral cough elixer, such as dextromethorphan, with inhaled steroids. Problems with such a design would include

difficulties in blinding and ethical issues related to the apparent deception of parents and children.

The final design-related problem which may have resulted in fewer subjects available for enrollment into the trial was a failure to adequately inform the medical community of the trial and enlist their support before beginning the recruitment effort. Efforts were made to enlist the support of those physicians working at the pediatric centre. These included several letters to all medical staff, informal discussions with high profile medical staff members and a presentation at the annual research forum. However, general practitioners were not informed of the project until after the recruitment effort had actually begun. The reason for this was that it was felt that all patients with clinical pertussis would be referred to the tertiary centre for nasopharyngeal swabs and so would be identified in the laboratory screening efforts. Such proved not to be the case and may have resulted in a loss of potential subjects for the investigation. The importance of informing physicians early in a recruitment effort has been emphasized by Croft et al. in their report on recruitment strategies employed in the Bogalusa Heart Study, a study to determine risk factors for cardiac disease in children. These authors successfully recruited between 80 and 93% of the entire pediatric population of the area under study using a combination of techniques directed at the community. The very first of these techniques was "the establishment of supportive and cooperative communication with all local physicians."<sup>97</sup> These recommendations have subsequently been confirmed by Petrovitch et al.<sup>98</sup> when reporting on their experience with screening and recruitment

for the systolic hypertension and the elderly program. These authors listed the need to inform the medical and lay communities about a recruitment effort early in an investigation, as well as the need to inform local medical associations of ongoing recruitment efforts, as two of twelve specific suggestions for improving recruitment in future collaborative trials.

### *Disease-related Problems*

In addition to recruitment problems stemming from the study design, there were also problems related to the particular disease under study. Some of these have been alluded to earlier, including the epidemic nature of pertussis infection and the acuity of onset of the illness. Other problems relating to pertussis itself include the potential confusion of symptoms of pertussis infection with those of other diseases and the seasonal variation in pertussis incidence which required concentration of recruitment efforts over a relatively short period of time each year. The absence of a laboratory-based gold standard for diagnosis and the lack of a sensitive and specific clinical case definition were also problematic.

In relation to the epidemic nature of pertussis, the problems this caused with the recruitment effort have been previously outlined. The absence of epidemic levels of pertussis infection during the years of the study meant that the numbers of infected children were significantly lower than in the previous year<sup>13, 14</sup>. This decreased the pool of patients available and therefore, decreased the numbers of subjects recruited.

Such problems are likely to be observed in any study of an infectious disease which exhibits epidemic qualities. Compounding these difficulties is the fact that the acute onset of whooping cough results in difficulties with recruitment efforts aimed directly at subjects in the community. Instead, one must rely on primary health care providers to correctly identify the problem and refer the subject as has already been described.

Problems such as these may be addressed in future studies by completing necessary planning and administrative work, such as securing ethics committees' approval in advance. This would mean that in the event of the appearance of epidemic rates of pertussis infection in the community, investigators could be ready to implement the recruitment phase of the trial. Such a project would best be undertaken by an established research group with adequate accessible funding to ensure that commencement of the project would not be hampered by the lack of readily available financial resources.

Other problems relating to pertussis which magnified recruiting difficulties include the absence of a sensitive and specific case definition and the absence of an adequate laboratory-based gold standard for diagnosis. The case definition used in our study was purposely designed to be broad with the only requirement being that the subject have a clinical history compatible with *Bordetella pertussis* infection. This must have included a history of paroxysmal coughing which may or may not have occurred following a period of catarrhal symptoms. The coughing paroxysms may or may not have been followed by vomiting, apnea, cyanosis, or an audible whoop. A study by Patriarca et al. to examine the sensitivity and specificity of various clinical case definitions of

pertussis showed that the presence of a paroxysmal cough for at least 7 days was only 54% sensitive and 77% specific when compared with culture results as the gold standard. This definition was not tested with serologic results as the gold standard<sup>99</sup>. Halperin et al.<sup>100</sup> tested a clinical case definition of pertussis which required the presence of cough for more than two weeks with vomiting, cyanosis, paroxysms, or apnea. Using data provided, the calculated sensitivity is 71% and the specificity is 65%. The gold standard in this investigation was the presence of any positive laboratory test (culture, direct immunofluorescence, or serology) for recent pertussis infection. It is difficult to apply these results directly to our study because the case definitions are different. Additionally, their literal interpretation is limited by the fact that the laboratory “gold-standards” employed to produce them are also flawed<sup>101</sup>, as discussed below. However, it is clear that the clinical diagnosis of whooping cough is imperfect. As is evident from our results, many subjects were excluded because they were not felt to meet the clinical case definition. It is quite possible that significant numbers of these subjects were actually infected and that their exclusion resulted in a group of “false negatives” in the application of our case definition as a clinical test. If such is the case, it would clearly have negatively affected recruitment.

Unfortunately, the lack of sensitivity and specificity for the diagnosis of pertussis is not limited to clinical case definitions. Laboratory methods for disease identification are equally problematic. Halperin et al. compared the results of various serological tests, culture of nasopharyngeal aspirates and direct immunofluorescence

against a “gold standard” of a positive result in any of the tests to determine the sensitivity and specificity of the various methods<sup>100</sup>. His group found that the sensitivity of nasopharyngeal culture was only 26%. This compared with a sensitivity of individual acute serological tests to two antigens (pertussis toxin and filamentous hemagglutinin) of 31%. Specificity of both tests was 100%, reflecting the choice of the gold standard. While paired (acute and convalescent) serology enhanced detection of positive cases to 88%, such an approach would not have been practical for our investigation because it required repeat testing three weeks after the initial serum sample. We needed to be able to randomize subjects from the time of our first contact with them. These findings indicate that while the use of laboratory tests can enhance the detection of pertussis infection, the practical utility of such information in a trial such as this one is limited. Consequently, our lack of serological testing is unlikely to have significantly influenced recruitment. Rather, recruitment was hampered by the lack of an adequate laboratory-based diagnostic test. McNicol and her colleagues examined the utility of immunofluorescent microscopy in the diagnosis of pertussis infection<sup>102</sup>. When compared with a “combination gold standard” of a positive pertussis culture *or* pertussis DNA as detected by polymerase chain reaction (PCR), the sensitivity of this method was only 32.3%, with a specificity of 97.1%. Consequently, even this method, had it been available to us, is unlikely to have improved our identification of subjects significantly.



### *Population-related Problems*

One of the most difficult things about this investigation was that members of the population to be studied were children. While data on the recruitment of children into clinical trials are sparse, that which exists consistently points to the practical and ethical difficulties with the recruitment process which are encountered when the subject is a minor<sup>103-109</sup>. In such a case the person giving consent is, by necessity, a surrogate. Introducing such a person into the decision process regarding study entry complicates that process considerably.

In discussing the difficulties associated with neonatal clinical trials, Mason uses words to the effect that “when their children are ill, parents may become anxious. They often experience feelings of powerlessness and may not understand medical arguments about the relative merits of one or another treatment made at such a time. Whether or not they agree to enter a trial, they may feel guilt as to whether or not they made the right decision”<sup>109</sup>. These sentiments are likewise implicit in an anonymous editorial published recently in *The Lancet*<sup>106</sup>. This editorial begins with a scenario meant to simulate a physician asking a mother to enter her newborn into a randomized, controlled trial and the mother subsequently discussing the matter with another person. The scenario is duplicated below:

“Your baby is very ill and may die. There are two ways of treating his illness, and we would like to include him in a trial that we are doing to find which treatment is better . Please sign this consent form.”

**“My baby’s very ill, and the doctor doesn’t know how to treat him! I don’t want them to experiment on my baby, but if I say ‘No’ they might be cross and not look after him properly - even though they deny this. And why do they want me to sign something? What are they up to? I can’t sort all this out at a time like this.”**

*The Lancet*, April 1, 1995

These are likely accurate reflections of the feelings of many parents when approached by investigators about entry of their child into a clinical trial. The impact of such feelings on recruitment rates for such investigations is unlikely to be positive.

While our trial did not deal with children who were critically ill, even parents of children with lesser degrees of illness experience doubts about the entry of their children into clinical trials<sup>103, 107</sup>. Interestingly, they seem more willing to allow their children to participate in cohort or observational studies. Kramer and Shapiro report that in their study of adverse drug reactions in a general pediatric group practice, 96% of the parents of the 3316 children visiting the practice agreed to participate. In comparison, when 132 of those parents agreeing to participate in the observational study were asked to participate in a randomized controlled study on the use of acetaminophen in febrile children, 34% of them refused<sup>103</sup>. This “experiment-related” anxiety has the potential to significantly limit enrollment of subjects from a pediatric population.

In addition to experiment-related anxiety, there may also be a hesitancy to be randomised. This is perhaps particularly true for a placebo controlled trial where one of the treatments is very unlikely to improve the patients’ medical condition (Hawthorne

and placebo effects excluded). Some parents may find this uncertainty unacceptable and refuse to enroll their child in a trial based on this feature alone<sup>90, 103</sup>.

In the case of our trial, the relatively heavy workload required by the parent may also have played a role in their refusal<sup>105</sup>. While the use of a spacer device such as an aerochamber™ and mask is not painful for a child, they often struggle and may cry during its use for the administration of inhaled medications. Our study protocol required the use of such a device for the administration of medication three times a day for 30 days. If parents had previous experience with these devices, they may have been hesitant to agree to such a treatment plan, either inside or outside the context of a clinical trial. This in turn may have adversely affected accrual rates for our study.

The fact that the investigators conducting the trial were unfamiliar to most of the patients and families referred for possible entry into the trial may have had an effect on patient recruitment. This was suggested by the fact that several of the parents contacted by the research nurse deferred entry into the trial until they had spoken with their general practitioner. Other investigators have also observed this phenomenon<sup>110</sup>. Postlethwaite and colleagues showed that patients often looked to their usual physicians for guidance when faced with decisions about embarking on a treatment plan for which there were no guaranteed benefits and for which the risks were non-negligible<sup>107</sup>. These authors reported the results of their efforts to recruit children into a clinical trial on the efficacy of growth hormone treatment in renal failure. They found that even when attempts were made to be completely neutral, some families requested advice and were

unable to make a decision without “help” from their attending physician. Therefore, the presence of a familiar physician, with whom a subject or his or her family has built a relationship, may be more likely to result in entry into the trial than refusal.

Perhaps most surprising of the population-related reasons for subjects contacted to be excluded from the trial was that of already being on inhaled or systemic steroids. This may reflect clinicians’ attempts to explain persistent cough in their pediatric patients on the basis of reactive airways disease. Presumably it did not reflect the presence of asthma in this group because all parents were asked if their children had asthma during the course of the screening interview. If the response was positive, they were asked to compare current symptoms with previous exacerbations of asthma. If symptoms were the same then the potential subject was excluded on the basis that he or she did not meet the clinical case definition and was, therefore, ineligible for inclusion in the study. While some patients with reactive airways disease do go on to exhibit symptoms consistent with asthma, there is a general hesitancy to label patients with this diagnosis if it is their first episode of symptoms<sup>111</sup>. Consequently, some practitioners prefer to use a therapeutic trial of anti-inflammatory medication usually combined with a bronchodilator in order to clarify the diagnosis<sup>112</sup>. Unfortunately, in patients with pertussis, this strategy is open to bias in that the inhaled steroid could potentially have a positive effect on either condition. There was no way to monitor such an effect as these patients were excluded.

The problem of subjects having to be excluded based on their already being on inhaled steroids was paradoxically compounded by one of our strategies to improve recruitment. At the information dinner held in the community for local general and family practitioners one of the co-investigators spoke about pertussis in general and discussed the trial, requesting that the doctors refer patients for enrollment so that they could be randomized. Unfortunately, following this information session, some of the physicians began treating their patients with clinical pertussis with inhaled steroids without referring them for randomization. This may reflect the reluctance of general practitioners to relinquish care to the tertiary centre<sup>90</sup>, or their discomfort with having their patients randomized to potentially receive a treatment which was unlikely to do good, namely placebo. Such a response is not uncommon, particularly in placebo-controlled trials<sup>105</sup>. Perhaps physicians felt that, given the clear absence of benefit of placebo, and the anecdotal acclaim for the potential benefit of steroids, referral for entry into the trial would be unethical. More likely is that the extra time involved in referring patients was not felt to be cost-beneficial<sup>90</sup>. They may have felt that, given that a study of inhaled steroids for use in pertussis was ongoing at the “tertiary centre,” risks were likely to be low and benefits potentially significant. Consequently, patients were started on inhaled steroids without being entered in the trial. Unfortunately, the exact number of patients for whom this was the case was not recorded in the study, nor was data on their response to treatment.

Perhaps this problem could have been avoided by presenting information to physicians in a different manner; a manner which emphasized flaws in previous studies on steroids to a greater degree. This, however, would be a delicate task. As pointed out in an article by Baum, “for a patient to be recruited, the clinician has to be in perfect equipoise about either of the two treatments being evaluated”<sup>113</sup>. To recruit under other circumstances Baum goes on to say, is ethically improper. While this view is extreme, there must be a balance between the potential benefits of the two medications being tested, or, in the case of placebo-controlled trials, between the benefits of the treatment and its risks. Consequently, emphasizing either risks or benefits to a greater or lesser degree may have had the same effect.

## **Review of Data Obtained**

Accepting that the number of subjects recruited for entry into the trial limits the generalizability of results, examination of findings is still valuable for hypothesis generation. Comparisons and contrasts with findings of other investigators further augments this utility. In the sections that follow, results obtained in the investigation will, therefore, be reviewed.

### *Baseline Characteristics*

The ages of subjects enrolled in the trial ranged from 2 to 95 months. While this differs from the ages of affected children reported in other trials<sup>10</sup>, these differences are likely primarily related to our inclusion criteria which required that children be less than 8 years old at entry. The older group was excluded because the disease tends to be more severe in the younger group<sup>114</sup>. The inconvenience of medication administration was, therefore, not felt to be worthwhile in the older group of children.

The number of days coughing before entry into the trial was similar between the beclomethasone and placebo groups, though those in the beclomethasone group had been coughing slightly longer than those randomized to the placebo group. The overall mean duration of coughing at entry into the trial was 14 days. This does not differ considerably from the duration of illness described by Zoumboulakis et al.<sup>81</sup> in their original study on the use of steroids in pertussis, though was slightly shorter than

that reported by Halperin et al <sup>10</sup>. The latter difference is again attributable to the inclusion criterion which required subjects to have less than 21 days of coughing at entry into the trial. This period was chosen because of the proposed mechanism of the steroid effect. As discussed, this is postulated to involve blocking of the infiltration of inflammatory cells into the airways with a resultant decrease in exfoliated cells and mucoid debris, and a subsequent reduction in cough. If such an effect were to have clinical value, given the relatively slow onset of action of inhaled steroids, patients would have to be treated early in the course of their illness.

The similarity between the duration of coughing at entry into our trial and that seen by Zoumboulakis et al. <sup>81</sup> is indicative of the ongoing difficulties experienced by physicians in diagnosing this illness. There continues to be a considerable lag time between the onset of symptoms and the clinical diagnosis of pertussis. Once diagnosed, however, patients with pertussis were identified by our project staff within a short period of time. This is supported by the relatively short mean duration of erythromycin therapy prior to study entry. Since erythromycin would not likely be the first-line therapy for most other bacterial respiratory infections, its use may indicate that the primary care physician was considering pertussis to be high on the differential diagnosis list. The short lag time between the time that erythromycin therapy was begun to the time subjects were entered therefore helps validate the identification method used for recruitment.

Despite the reported increased prevalence of pertussis in girls <sup>2</sup>, equal numbers of male and female subjects were recruited for this investigation.



The relatively high percentage of subjects reporting atopic disease represents a potential source of bias in the study. Children with respiratory illness in the first 2 years of life have an increased risk of asthma when atopic disease is present in themselves or a first degree relative <sup>111</sup>. Consequently, despite efforts to exclude children with symptoms of asthma from enrollment during the screening interview, several of those recruited may have been manifesting symptoms of asthma, rather than pertussis. However, 6 of the 8 subjects who reported atopic disease had positive pertussis swabs, indicating that they were truly infected. Hence, another explanation for the high proportion of atopic individuals in the sample population is that these individuals may have been predisposed to the development of pertussis.

Attendance at daycare was similar in both groups and did not differentiate between subjects with positive and negative pertussis swabs.

### *Baseline Symptoms*

The numbers of subjects exhibiting various pertussis-related symptoms seen in our study were similar, though not identical to those of other investigators. In our study, 72% of subjects exhibited vomiting as part of their symptomatology. This compares with 76% seen by Halperin et al. (1989) in their study of Nova Scotian children <sup>10</sup>. In contrast, 72 % of our subjects exhibited whooping as compared with 58% of those in the study by Halperin et al. Likewise, only 17% of our subjects exhibited apnea, with a further 17% showing parentally-recognized cyanosis. This compares with 23% and 29%

respectively in the Nova Scotia study. While these differences are small and likely a function of the low numbers of subjects recruited, given the younger age of subjects in our study, the lower incidence of apnea and cyanosis is somewhat surprising.

### *Laboratory Findings*

Laboratory findings in this study were consistent with expected results in that chest X-ray and complete blood count (CBC) findings can be variable and of variable etiology<sup>1</sup>. Hence, the absence of leucocytosis and lymphocytosis in those patients for whom CBC's were ordered does not preclude the diagnosis of pertussis. Chest X-rays were performed in a greater proportion of subjects in this investigation than in those reported by Gordon et al<sup>66</sup>. These researchers reviewed all subjects presenting with a diagnosis of pertussis to the Hospital for Sick Children in Toronto over an 11 year period. They found that 20% of patients diagnosed with pertussis had a chest X-ray performed. This compares with almost twice that proportion in our study. The proportion of subjects with pneumonia was similar to that reported by Gordon et al. Fourteen per cent of subjects X-rayed in our study showed radiological evidence of pneumonia while 12% of patients in the group Gordon et al. studied exhibited such findings. The Toronto group did not report any X-rays as showing peribronchial thickening, which was the most common abnormal finding in X-rays on subjects in this investigation, being present in 28% of those for whom X-rays were taken.

### *Follow-up Calls*

The purpose of these calls was to encourage ongoing participation, to assess progression and complications of the disease, and to assess potential side effects of medications. While parents of most subjects enrolled in the present study continued to participate in the trial throughout its duration, 5 parents opted to remove their children from the study prior to completion. This represents a retention rate of 78%, close to the 80% retention estimated in calculating the sample size. This observation suggests that the follow-up calls were at least partially helpful in encouraging parents to leave their children in the trial. A detailed discussion of the reasons for removal of subjects and subsequent handling of data follows later in this section and will not be reiterated.

In assessing the progression and complications of disease, the follow-up calls did not provide any useful information beyond that provided by the cough diaries after the second call on day 16. Prior to this, a number of subjects were experiencing intercurrent illnesses which were treated in various ways by their family physicians. This information would have been lost if the first and second calls had not been made. Had the number of subjects been larger, this information would have been important to have, particularly if the medications used were potential sources of bias. In the present investigation, such factors likely had little effect on the outcome of interest.

The follow-up calls did show a cessation of whooping in all subjects by day 16 of the trial. Since the day that whooping started was not recorded, conclusions about the duration of this symptom in our population and comparisons of this data with

that of other investigators is not possible. However, results were consistent with expected findings in that whooping disappeared well before resolution of the cough<sup>62</sup>. No difference in the relative times for disappearance of whoops and apneas between the two groups was detected. We did not quantify daily occurrence of whoops or apneas so differences in the actual times it took for these features to disappear are not reported. The number of subjects enrolled was far too small to detect any of the rare complications of whooping cough.

One interesting feature was the development of otitis in one of our patients with culture-positive pertussis. While not commonly reported, this is not an unusual finding in pediatric patients with pertussis. The usual organism is *Streptococcus pneumoniae*<sup>1</sup>. This being the case, it is unusual that our patient failed to improve despite multiple anti-Streptococcal antibiotics. One explanation is that there was some persistent serous effusion following the acute infection which was interpreted by the family doctor as ongoing suppurative disease.

The complications of study medications which were of interest to the investigators were the appearance of candidal mouth infection (thrush) and change in voice. In addition, we sought to identify any unrecognized complications which might result from the use of inhaled beclomethasone in this therapeutic setting. No medication-related complications were reported during the course of the follow-up calls. The single subject who experienced thrush was taking placebo. The other complications reported on

the first and second follow-up calls were not attributable to beclomethasone or placebo by any known mechanism of action and therefore, were treated as coincidental.

### *Cough Duration*

The duration of coughing was the primary outcome variable for this investigation. Overall, subjects coughed for an average of 38 days (median of 40 days) from the time of onset of their symptoms. This is slightly shorter than the duration of coughing reported by Bortolussi et al<sup>62</sup>. They found a median total cough duration of 48 days in immunized Canadian children. Reasons for this difference likely relate to differences in the populations studied. The inclusion/exclusion criteria for our study mandated the exclusion of those who had been coughing longer than 21 days. This may have resulted in a slightly lower mean (and median) duration of symptoms. Additionally, in our study, subjects were not followed after their 30 day treatment course. Fifty-five percent of our subjects continued to cough more than once per day at the end of this course. The duration that the cough persisted after the treatment ended is unknown. It is possible that if we had followed subjects to the disappearance of cough then similar results would have been obtained. The finding is potentially significant only in that it may mean that future researchers should follow children longer in order to document the clinical effect of a particular therapy.

Following entry into the study and commencement of medication, the mean duration of coughing for the placebo-treated group was 21.4 days while that in the

beclomethasone-treated group was 26.8 days. While these results did not achieve statistical significance, the fact that the duration of coughing in the placebo-treated group was shorter than that in the group receiving active treatment suggests that inhaled beclomethasone may make patients with whooping cough worse.

Winrow recently reported a study in which pediatric pertussis patients were treated with inhaled, nebulized budesonide twice daily with resultant disappearance of apneas within 24 hours and improvement in "cough score" within 72 hours<sup>80</sup>. Though not randomized or blinded, this paper suggested a role for inhaled steroids, particularly in the treatment of infants with pertussis. Other investigators as previously discussed, have found that oral or injected steroids may have a beneficial effect<sup>78,80-84</sup>. Our study contrasted these results in showing no benefit to inhaled steroids in the treatment of this condition.

Possible reasons for the divergence in findings include the possibility that no treatment effect exists and that the study results accurately reflect the effects of inhaled steroids on the respiratory tracts of patients with whooping cough. Other explanations include the non-negligible possibility of a type II error due to differences in the groups of subjects at entry into the trial, problems with compliance, and the low numbers of subjects successfully recruited. Additionally, differences in dosage, route, method, and duration of medication administration in comparison with previous studies, as well as differences in the populations studied may have played a role.

While it seems most likely that no positive treatment effect exists, particularly in light of the trend towards better performance in the placebo group, there is a strong possibility that we have committed a Type II error. There are several potential explanations for why this may be so. First, more patients in the placebo group were culture-negative than in the beclomethasone group. The sensitivity of nasopharyngeal culture in pertussis is estimated to range from 26-80% when compared with a variety of other markers for infection, including serological tests and clinical criteria<sup>100, 115</sup>. However, it is up to 100% specific<sup>100</sup>. Therefore, despite efforts to ensure that patients enrolled in the study actually had whooping cough, it is possible that some members of the placebo group who were culture-negative actually had simple viral or post-viral coughs. If such were the case, then these patients would have been expected to improve more rapidly than those with true whooping cough.

Despite the randomization process the beclomethasone-treated patients may have been sicker than the placebo-treated patients at entry into the trial. The beclomethasone patients had been coughing longer and were coughing more frequently than the placebo patients when the trial began. This being the case, they may have been expected to take longer to improve so that any observed effect would again be diminished. This latter possibility seems less likely in light of the similarity in the time it took subjects in each group to achieve a 25% decrease cough frequency. If the absence of a treatment effect on the duration of coughing in the beclomethasone-treated subjects had

been due to those patients being more ill, then the time to a 25% decrease in symptoms would be expected to be shorter for this group.

Compliance may also have played a role. While there was little observed difference between the group compliance rates, 4 of the patients treated with beclomethasone failed to return their inhalers. Some investigators consider failure to return medication as an indicator of general non-compliance, even to the point of excluding such people from entry into a trial<sup>103</sup>. Such a process would not have been appropriate in this type of trial<sup>105</sup>. Other investigators observed that an average of 20-25% of patients failed to return medication containers, though felt that this did not preclude them from analysis<sup>116</sup>. In the case of this trial, the lack of compliance with the study protocol may reflect a lack of compliance with medication administration, thereby making the actual compliance rate in the beclomethasone group significantly less than that calculated. If this is the case, then any observed treatment effect in this group would necessarily be blunted.

Even the estimation of the required sample size may have been problematic in that assumptions made may have been flawed. The mean duration of coughing used to estimate  $\Delta$  (the anticipated change in cough duration which would be clinically significant), as well as the standard deviation of this value were taken from the study by Zoumboulakis et al<sup>81</sup>. The mean duration of coughing in that study after entry into the trial was 19.3 days with a standard deviation of 6.5 days. For our trial, we found a mean duration of coughing in the placebo group of 21.4 days with a standard deviation



of 11.7 days. Using these numbers in the formula for sample size shows that even if the power was reduced to 80%, 85 subjects would be required in each group in order to detect a 25% decrease in the duration of coughing. This number of subjects is too large to be realistically recruited from a smaller centre such as ours, and may have resulted in our trying to organize a multicentered trial, had it been anticipated.

The most problematic aspect of this study, is its lack of power. The difficulties experienced in recruiting resulted in low numbers in each treatment group, and subsequently, a decrease in power. The tendency towards an improvement in the placebo group prevents the use of a formal *post hoc* power calculation. Consequently, even though the study has not shown a positive effect, the possibility that one exists can not yet be definitively ruled out. The tendency for more rapid improvement in the placebo group, however, makes this possibility more unlikely. Given results thus far, in order to show statistical significance in this trial, remaining subjects would have to demonstrate an average difference of 6.1 days less coughing in the beclomethasone group than in the placebo group.

Differences in dosage, route, method and duration of medication administration may also explain the differences in our findings and those of other investigators. The only other trial of inhaled steroids<sup>30</sup> used budesonide rather than beclomethasone, in a dose of 500 mcg twice daily for those less than 2 years old and 1 mg twice daily for those older than 2 years. The author reports only administration by “standard nebulization technique” without specifying whether this meant delivery by wet

nebulization or delivery by metered dose inhaler. The duration of treatment is not specified but lasted “up to four weeks” in some cases. The treatment was effective in the abolition of apneas within 24 hours but resulted in only improvement in “scoring systems for cough....coughing was not completely abolished.”<sup>80</sup>. While the dosages used by this author may be similar to ours when differences in potency are taken into account, if the medication were administered by wet nebulization, then it is possible that variations in medication delivery to the tissues are responsible for the therapeutic effects observed. It may also have been the nebulization solution (for example, normal saline) that effected the improvement in symptoms through the improvement of pulmonary toilet. Further comparison of our findings to those of the Winrow study<sup>80</sup> is difficult due to the general lack of information about the population studied and the interventions used.

In considering results of other studies on the use of steroids in pertussis in relation to ours, a number of important differences are evident. For all of the other studies, while the duration of therapy was shorter than that in our study, the route of administration was oral or parenteral and the potency of the preparation used was much stronger<sup>117</sup>. Chandra et al.<sup>82</sup> used oral betamethasone in combination with chloramphenicol for an unspecified period of time to treat Indian children with pertussis, while Zoumboulakis<sup>81</sup>, in the first placebo-controlled trial on steroids in pertussis, used intramuscular hydrocortisone daily for 7-8 days. Subsequent studies have employed oral prednisolone for 5 days<sup>81</sup>, oral betamethasone three times daily for 10 days<sup>84</sup> or 14 days<sup>78</sup> and oral dexamethasone daily for 4 days<sup>85</sup>. All but one<sup>85</sup> demonstrated a beneficial effect

in the groups treated with the steroid preparation. It may be that the short burst of strong anti-inflammatory activity obtained from oral or parenteral steroid preparations is more efficacious in preventing damage to the respiratory mucosa than inhaled preparations which have a relatively slower onset of action. It is equally possible that the inhaled agent acted as an irritant to the already inflamed airway so that any beneficial effects from the anti-inflammatory properties of the medication were negated. Such an effect would not have been evident with the oral or parenteral preparations.

#### *Disease Impact and Severity*

While again limited by the numbers of subjects enrolled, results of the disease impact questionnaire administered at the end of the study support other work by Mark and Granstrom in 1992<sup>4</sup>. Their study showed that 54% of affected children had disturbed sleeping habits related to their illness. The same was true for 78% of parents. This group also reported that 55% of mothers and 34% of fathers had to stay home from work because of their child's illness. Our group had more extreme results with 94% of parents reporting illness-related sleep disturbance in both themselves and their children. In contrast to other author's findings, however, only 17% of parents reported having to take time off work because of their child's illness. This may be a reflection of the economic climate of the region. No statistical difference was seen in the reported impact in the placebo group as compared with the beclomethasone group. These findings indicate that despite virtually universal vaccination, pertussis continues to represent a

significant burden to the children and families afflicted with it. The need to find effective treatments for these children is even more apparent in the face of such evidence.

### *Other Issues*

In addition to its direct findings, the study also highlighted a number of other points. The first is the difficulty in making an accurate clinical diagnosis of pertussis. While other investigators have relied on the use of the direct immunofluorescence<sup>10, 100</sup> or polymerase chain reaction (PCR)<sup>118</sup>, these tests were not routinely available at the Janeway laboratory and their cost was beyond the scope of our budget. Consequently, we relied on other physicians' clinical diagnosis with culture confirmation for case identification. As shown in table 4.1, after a review of symptoms by the investigators or the research nurse, 28.4% of patients referred for a pertussis swab did not have a clinical history consistent with classical pertussis infection. This has implications for future researchers in that before any treatments can be effectively tested, pertussis must be able to be diagnosed with certainty in the target population. At present, there appears to be no diagnostic tool available to practitioners which will allow them to make a definitive diagnosis of pertussis. Future work should, therefore, concentrate on finding a more reliable diagnostic test. If such a test is not found, then the inclusion of only culture-positive subjects in future therapeutic trials represents the most practical and scientifically valid alternative.

A surprising outcome from the study was the revelation of the number of patients with pertussis being treated in the community with oral or inhaled steroids. For the culture positive group, this was the most common reason for exclusion from the study. It is unknown whether this is a reflection of the background prevalence of asthma and reactive airways disease, on which a pertussis epidemic was transposed, or whether it represents general practitioners' misinterpretation of information sent out by the investigators about the study. If the latter is true, it underscores the necessity of providing full and accurate information when recruiting patients into a clinical trial. It also emphasizes the potential dangers of relying on anecdotal evidence for clinical decision-making. In this case, patients were treated with a relatively innocuous medication without definite ill effect. Applied to other situations, however, the practice could have more significant consequences.

### *Future Directions*

Despite our efforts, the question of the utility of steroids, both inhaled and systemic, to treat patients with pertussis remains unanswered. Other studies will be required and will need to address some of the deficiencies in our project if they are to effectively answer the question. Based on the experience with this project, the following recommendations are made for future initiatives.

Recruitment strategies should be established in advance with an adequate budget allotted to recruitment efforts. These efforts should include advance information

to physicians and health professionals in the community, community advertising to alert the public about the project and frequent follow-up calls to ensure ongoing cooperation with the trial<sup>90, 97</sup>. It would be helpful to have a staff member assigned to this job alone<sup>90, 105</sup>. During the recruitment effort, records should be kept of all referrals received, contacts made and their disposal, including the reason for their exclusion if they are ineligible<sup>90, 105</sup>. If only culture positive children are included, the recruitment effort could be simplified significantly by focussing efforts on the microbiology laboratory. If telephone contact with potential participants is required then persistence and spreading calls evenly throughout the week, including some calls on weekends should be employed to maximize the yield<sup>96</sup>. If smaller centres wish to initiate a project then they should consider involving other centres in the effort, as a multicentered trial would allow for greater numbers of subjects to be recruited<sup>105</sup>. Alternately, preparing a protocol for implementation at the time of a pertussis epidemic would also be effective.

An appropriate outcome measure for future trials would be the disappearance of cough and should be collected prospectively by direct questioning of parents. This could take the form of a telephone call every two days. Such an outcome would decrease the burden of the study for parents and might increase compliance.

Consideration should be given to conducting another trial on the utility of inhaled corticosteroids in the treatment of pertussis, since our data were unable to definitively answer that question. Alternately, since the most dramatic results have been seen with systemic steroids and given that subjects in our trial who were treated with

steroids coughed longer than those treated with placebo, future studies on the efficacy of steroids in pertussis should consider focussing on the effect of a short burst of systemic steroid therapy. The side effects of such a treatment are likely to be minimal and the benefits may be significant. A multicentered trial would not be necessary if the investigation were conducted during an epidemic year and adequate recruitment were ensured.

More work should be done in the area of pertussis diagnosis. The lack of a rapidly available diagnostic test is a major hindrance to research on this not uncommon disease. In the interim, inclusion in therapeutic trials should be contingent on isolation of *Bordetella pertussis* from a culture of nasopharyngeal aspirate. The specificity of this test ensures that treatment effects seen will be applicable to the population with clinical pertussis confirmed by any laboratory method.

### **Summary of Findings**

In summary, this study has highlighted the difficulties in pertussis research, particularly from the point of view of case definitions, diagnosis and defining and measuring an outcome variable. Additionally, it has re-emphasized the importance of an effective recruitment strategy in clinical trials research, and provided new insights into some of the difficulties encountered in implementing such a strategy in the pediatric population. In doing so it has allowed the development of a template for research into

treatments for pertussis which can be used to plan future studies, thereby avoiding many of the problems encountered in this one.

The results of the study, while limited in their power and generalizability by the low numbers of subjects enrolled, suggest but do not prove that inhaled steroids are not effective in reducing the duration of paroxysmal coughing in pediatric patients with pertussis. The study also suggests that inhaled steroids do not result in more rapid improvement in other symptoms nor do they significantly lessen the impact of disease on child and parental sleep, or time lost from work. Future research on this question will be required before it can be definitively answered.



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## **Appendices**

## **Appendix A**

### **Centre-Specific Recruitment Letter**

## Memo

**To:** Janeway Pediatricians, Pediatric Residents, Casualty Officers, Marion Yetman  
(Infection Control Officer)

**From:** Dr. Andrew Warren, Resident  
Dr. A.R. Cooper

**Re:** Pertussis Study

---

After much preparation, we are finally ready to start recruiting patients for our study on the use of inhaled steroids to decrease coughing in pediatric patients with pertussis. The study is a randomized, double-blind clinical trial to examine the utility of inhaled steroids in decreasing the duration of coughing in patients with pertussis. Patients who are enrolled will be randomly assigned to receive either inhaled steroids (beclomethasone 200mcg tid by aerochamber and mask) or placebo (demonstrator inhalant two puffs tid by aerochamber and mask) for one month (30 days). The parents will be asked to keep a diary of the child's coughing episodes. They will also be telephoned several times during the course of the study and asked to answer some questions about the child's progress. All medications are, of course, supplied free of charge. Both inpatients and outpatients are eligible for inclusion.

We are requesting your help in recruiting patients to this study. The target number is 80, with accrual being accomplished over 2 years. Attached is a copy of the specific inclusion and exclusion criteria we are using. If you see any patients with clinical or laboratory-diagnosed pertussis, please let us know. We have acquired the assistance of Marilyn Harvey, RN as a research nurse, which should make contact with the patients fast and efficient.

Should you have a patient you wish to refer, please page Andrew Warren or call Marilyn at extension 567. Thanking you in advance for your anticipated cooperation.

**Inclusion / Exclusion Criteria****Inclusion Criteria:**

- Age 0-7 years. yes \_\_\_\_ no \_\_\_\_
- Early disease (ie. less than 14 days of paroxysmal coughing). yes \_\_\_\_ no \_\_\_\_
- Clinical history compatible with *Bordetella pertussis* infection.  
(must include a history of paroxysmal coughing which may or may not occur following a period of catarrhal symptoms. The coughing paroxysms may or may not be followed by vomiting, apnea, cyanosis, or an audible whoop.)  

**OR**

yes \_\_\_\_ no \_\_\_\_
- A positive culture for *Bordetella pertussis*.

**Exclusion Criteria :**

- Refusal to participate. yes \_\_\_\_ no \_\_\_\_
- Presently on steroids for other purposes (eg. asthma or rheumatic disease). yes \_\_\_\_ no \_\_\_\_
- History of active or quiescent pulmonary tuberculosis. yes \_\_\_\_ no \_\_\_\_
- History of untoward reaction to beclomethasone. yes \_\_\_\_ no \_\_\_\_

If the answer to any of the conditions in the inclusion criteria is no, patient is ineligible.

If the answer to any of the conditions in the exclusion criteria is yes, patient is ineligible.

Any question regarding patient eligibility should be discussed with investigators.

## **Appendix B**

### **General Practitioner Recruitment Letter**





Janeway Place  
St. John's, Newfoundland  
Canada A1A 1R8 34

January 18, 1995

Telephone 709-778-4222  
Facsimile 709-778-4333

Dear Doctor:

This letter is to ask for your assistance in recruiting patients for a study which we have undertaken at the Janeway to test the efficacy of inhaled steroids in the treatment of pertussis. A number of articles have suggested that systemic steroids are useful in reducing the number and duration of coughing episodes in pediatric patients with this disease. Inhaled steroids, by virtue of their localized action and low side effects profile might therefore be expected to be even better.

Those that agree to participate will be given either a steroid (beclomethasone) inhaler or a placebo inhaler which they will use t.i.d. for a total of one month. During that month they will be asked to record the total number of coughing episodes in a cough diary which will be given them. The end point of the study is the cessation of coughing as defined by less than or equal to one coughing episode per day. All patients will also be treated with erythromycin for 14 days, as recommended by the Canadian Pediatric Society.

Inclusion / exclusion criteria are listed on the back of this letter. If you see a patient with whooping cough, it would be much appreciated if you would send the child to the Janeway to have a pertussis swab taken. This will allow us to identify them (through the laboratory records) and offer them the opportunity of participating in the study. Additionally, if you are contacted by any of your patients regarding this study, your positive support would also be appreciated.

If you have further questions or concerns about this study, please contact one of the undersigned through the Janeway switchboard (778-4222). Thanking you in advance for your anticipated support in this matter.

Yours sincerely,

A.R. Cooper, MD, FRCP(C)  
Pediatrician

Andrew Warren, MD  
Resident

## **Appendix C**

### **Cough Diary**

---

**PATIENT  
COUGH  
DIARY**

**ID #** \_\_\_\_\_

**IF FOUND, PLEASE RETURN THIS  
DOCUMENT TO:**

**DR. ANDREW WARREN  
JANEWAY CHILD HEALTH CENTRE  
PHONE: 778-4222**

---

Please record your child's coughing episodes in the boxes below. Use a stroke to record each episode. For example, a child who has 12 coughing episodes per day would have a box that looked like this:

~~||||~~ ~~||||~~ ||

It is important to only record episodes you know about. If you forget to record on a particular day, just write "forgot" and carry on with the next day.

day 1	day 11	day 21
day 2	day 12	day 22
day 3	day 13	day 23
day 4	day 14	day 24
day 5	day 15	day 25
day 6	day 16	day 26
day 7	day 17	day 27
day 8	day 18	day 28
day 9	day 19	day 29
day 10	day 20	day 30

## **Appendix D**

### **Data Collection Forms**

Initial. \_\_\_\_\_ 139  
Chart #: \_\_\_\_\_  
Study #: \_\_\_\_\_  
Entry date: \_\_\_\_\_

## DATA COLLECTION FORM

### Demographics

Source of referral: lab \_\_\_\_\_ emerg \_\_\_\_\_ pediatrician \_\_\_\_\_ GP office \_\_\_\_\_

Age: \_\_\_\_\_ years \_\_\_\_\_ months

Sex: \_\_\_\_\_ male \_\_\_\_\_ female

Daycare attendance: \_\_\_\_\_ yes \_\_\_\_\_ no

Vaccinations: \_\_\_\_\_ up to date

\_\_\_\_\_ partially vaccinated (details) \_\_\_\_\_

\_\_\_\_\_ unvaccinated

Does your child have asthma? \_\_\_\_\_ yes \_\_\_\_\_ no / Allergies \_\_\_\_\_ yes \_\_\_\_\_ no / eczema \_\_\_\_\_ yes \_\_\_\_\_ no

### Disease Characteristics

Date of onset of coughing \_\_\_\_\_

day/month/year

Which of the following symptoms does he/she have currently (tick all that apply)

coughing episodes \_\_\_\_\_

vomiting \_\_\_\_\_

whoops \_\_\_\_\_

stopping breathing (apneas) \_\_\_\_\_

turning blue \_\_\_\_\_

fever \_\_\_\_\_

Which of the following investigations has your child had completed?

nasal swab \_\_\_\_\_

results: \_\_\_\_\_

chest x-ray \_\_\_\_\_

results: \_\_\_\_\_

CBC \_\_\_\_\_

results: WBC \_\_\_\_\_ % lymphs \_\_\_\_\_ ALC \_\_\_\_\_

other tests (details): \_\_\_\_\_

### Treatment

How many days has your child been receiving erythromycin prior to now (write 0 if not on erythromycin at present) \_\_\_\_\_

Has your child been on another antibiotic besides erythromycin? \_\_\_\_\_ yes \_\_\_\_\_ no

If yes, what was/ is it and what was/is the dose? \_\_\_\_\_

Is your child currently on any other medication besides that mentioned above ( for example puffers, etc.)? If yes, please provide details \_\_\_\_\_

### Complications

Since becoming ill, has your child had - pneumonia \_\_\_\_\_ yes \_\_\_\_\_ no

-seizures \_\_\_\_\_ yes \_\_\_\_\_ no

-any other complications which your doctor has attributed to whooping cough? (details) \_\_\_\_\_

Initial: \_\_\_\_\_ 140  
Chart #: \_\_\_\_\_  
Study #: \_\_\_\_\_  
Entry date: \_\_\_\_\_

**DATA COLLECTION FORM  
FOLLOW-UP**

**Disease Characteristics**

Which of the following symptoms does he/she have currently (tick all that apply)

coughing episodes \_\_\_\_\_

vomiting \_\_\_\_\_

whoops \_\_\_\_\_

stopping breathing (apneas) \_\_\_\_\_

turning blue \_\_\_\_\_

fever \_\_\_\_\_

**Complications**

Since becoming ill, has your child had - pneumonia \_\_\_\_\_ yes \_\_\_\_\_ no

-seizures \_\_\_\_\_ yes \_\_\_\_\_ no

-any other complications which your doctor has attributed  
to whooping cough?

(details) \_\_\_\_\_

Is your child currently experiencing:

thrush \_\_\_\_\_

\_\_\_\_\_ yes \_\_\_\_\_ no

change in voice \_\_\_\_\_

\_\_\_\_\_ yes \_\_\_\_\_ no

other symptoms not listed above (details): \_\_\_\_\_

Initial: \_\_\_\_\_ 141  
Chart #: \_\_\_\_\_  
Study #: \_\_\_\_\_  
Entry date: \_\_\_\_\_

### EXIT ADDENDUM

Do you feel this illness has resulted in significance sleep disturbance for your child? \_\_\_\_ yes \_\_\_\_ no  
for you? \_\_\_\_ yes \_\_\_\_ no

Has this illness required you or another caregiver to take time off work to look after your child?  
\_\_\_\_ yes \_\_\_\_ no

If yes, How many days? \_\_\_\_\_

How would you rate the overall severity of your child's illness on the scale below?

1	2	3	4	5
mild (like a cold)		moderate		severe (life threatening)

**THANK YOU FOR YOUR COOPERATION IN THE STUDY!!**



**Appendix E**

**Consent Form**

## CONSENT TO PARTICIPATE IN BIO-MEDICAL RESEARCH

**TITLE:** The Short-term Use of Inhaled Beclomethasone in Patients with Pertussis : A Randomized Clinical Trial

**INVESTIGATORS:** Dr. Andrew Warren  
Dr. A.R. Cooper  
Dr. John Hamett

Your child or ward has been asked to participate in a research study. Participation in this study is entirely voluntary. You may decide not to allow your child to participate or may withdraw from the study at any time without affecting your normal treatment.

Confidentiality of information concerning participants will be maintained by the investigators. The investigator will be available during the study at all times should you have any problems or questions about the study.

### Purpose

The purpose of this study is to determine whether the short-term use of inhaled beclomethasone to treat patients with pertussis (whooping cough) reduces the duration of coughing episodes significantly more than treating them with an inhaled non-toxic "fake-drug" known as a "placebo."

### Procedures:

If you agree for your child/ward to participate in the study, you will be asked to answer some questions regarding your child's illness by one of the investigators or his delegate. The questionnaire is short and should take only about 5-10 minutes to complete. After completion of the questionnaire, your child/ward will be randomly assigned to receive one of two possible treatments, which he/she will receive three times per day for one month. You will be responsible for administering this treatment which consists of either 1) inhaled beclomethasone (a steroid preparation usually used to treat patients with asthma) or 2) an inhaled placebo as described above. You will not know the treatment to which your child has been assigned, nor will the investigator until the study is over. Both treatments are safe. Over the following month you will be asked to record the number of coughing episodes per

day which your child experiences in a cough episode diary which you will be given. If your child goes to school, we will ask you to give the diary to his/her teacher to record daytime episodes. In addition, you will be contacted 8 times by telephone so we may check your child's progress. On the first 7 occasions you will be asked 6 short questions. These should take less than 5 minutes to answer. On the final occasion you will be asked several new questions relating to your estimation of the seriousness of your child's disease. This final questionnaire should take only 10 minutes to complete. Arrangements will also be made at that time for the return of puffers to the study coordinator. At the end of the study, cough diaries and answers from parents of children receiving both beclomethasone and placebo will be compared to see if there is a difference.

In addition to the inhaled medication, all study participants will be treated with erythromycin (or alternative antibiotic if they are allergic) for 14 days as part of the standard treatment for pertussis.

#### Possible risks, discomforts, or inconveniences

Risks from either of these treatments are minimal. However, there is a slight risk that if your child is assigned to the steroid group, a slight facial rash, temporary changes in voice, mouth or throat irritation, or oral thrush (white mouth) may appear. This can be avoided by wiping the face and rinsing the mouth after each treatment. Since no one will know which children are getting the steroids until the end of the study, everyone will have their faces wiped and be asked to rinse their mouths after treatment.

The only discomfort involved will be the use of the aerochamber and mask three times daily. This is not painful but younger children may struggle a little during administration. Most children tolerate it without much difficulty.

#### Alternative procedures or treatment for those not entering the study

If you choose not to participate in the study your child will be treated in exactly the way children with pertussis are usually treated. That is, with antibiotics (to prevent further spread of the organism) and supportive care. Other treatments are not standardized but some physicians may use inhaled steroids. Your refusal to participate in the research project will not affect your child's treatment in any way.

Your signature on this form indicates that you have understood to your satisfaction the information regarding your participation in the research project and agree to the participation of your child/ward as a subject. In no way does this waive your legal rights nor release the investigators, sponsors, or involved institutions from their legal and professional responsibilities.

I, \_\_\_\_\_, the undersigned, agree to the participation of \_\_\_\_\_, (my child/ ward) in the research study described.

Any questions have been answered and I understand what is involved in the study. I realise that participation is voluntary and that there is no guarantee that I will benefit from my involvement. I acknowledge that a copy of this form has been given to me.

Signature of Parent/Guardian \_\_\_\_\_ (Date) \_\_\_\_\_

Relationship to Participant Named Above: \_\_\_\_\_

\_\_\_\_\_  
Witness Signature

\_\_\_\_\_  
Date

To be signed by investigator:

To the best of my ability I have fully explained to the subject the nature of this research study. I have invited questions and provided answers. I believe that the subject fully understands the implications and voluntary nature of the study.

\_\_\_\_\_  
Signature of Investigator)

\_\_\_\_\_  
(Date)

Phone Number: 778-4222 (page)

(Signature of Minor Participant) \_\_\_\_\_

(Age ) \_\_\_\_\_

## **Appendix F**

### **Letter Informing Attending Physicians of Patient Enrollment**

Date: \_\_\_\_\_

Dear Dr. \_\_\_\_\_:

Your patient, \_\_\_\_\_, has entered a randomized, double blind, placebo-controlled clinical trial to test the efficacy of inhaled steroids in patients with clinically-diagnosed or laboratory-diagnosed whooping cough.

The treatment being evaluated consists of two puffs of inhaled steroid (beclomethasone) or two puffs of inhaled placebo (propellant only) three times a day for 30 days. These are administered in a double-blind manner such that neither the investigator nor the patients/parents know which "drug" they are taking. Parents are asked to keep a diary of the child's coughing episodes, which will be used as the primary outcome measure. They are also being contacted at regular intervals to check on the progress of their child's coughing.

Should you have any further questions about the study, or if, for *emergency* reasons, you need to know which of the two drugs the patient is on, please contact Dr. A.R. Cooper or Dr. Andrew Warren through the Janeway switchboard (Ph. 778-4222).

Your cooperation and support is greatly appreciated.

Sincerely,

Andrew Warren, MD

A.R. Cooper, MD, FRCP(C)

## **Appendix G**

### **Human Investigations Committees Approval Letters**



# Memorial

University of Newfoundland

Human Investigation Committee  
Office of Research and Graduate Studies (Medicine)  
Faculty of Medicine, The Health Sciences Centre

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February 2, 1995

**Reference #94.155**

Dr. Andrew Warren  
Paediatric Resident  
Janeway Child Health Centre

Dear Dr. Warren:

This will acknowledge receipt of your correspondence dated **January 25, 1995**, wherein you provide a revised consent form for the research study entitled "**The Use of Inhaled Steroids to Treat Paediatric Patients with Pertussis**".

I have reviewed the information provided and now wish to advise that I am recommending full approval of the application.

This decision will be ratified by the full Human Investigation Committee at a meeting scheduled for **February 9th**.

We take this opportunity to wish you every success with your research study.

Sincerely yours,

H/B. Younghusband, Ph.D.  
Chairman  
Human Investigation Committee

HBV/jglo

cc: Dr. J. Harnett  
Dr. R. Cooper  
Dr. K.M.W. Keough, Vice-President (Research)  
Dr. Wayne Andrews, Chairman, Ethics Committee, Janeway Hospital  
Dr. Kevin Hogan, Medical Director, Janeway Hospital



1994 12 19

Janeway Place  
St. John's, Newfoundland  
Canada A1A 1R8

150

Telephone 709-778-4222  
Facsimile 709-778-4333

Dr. A. Warren  
c/o Janeway Child Health Centre

Dear Dr. Warren:

**Re: Short Term Use of Inhaled Beclomethasone to Reduce Duration of Paroxysmal Coughing in Pediatric Patients with Pertussis**

I am writing to advise you that your proposal was reviewed by the Janeway's Human Investigation Committee and that it is:



approved



approved with the following questions, observations or limits (see attached)



deferred pending receipt of additional information (see attached)



deferred pending your personal review of this proposal at the next Human Investigation Committee meeting.



not approved.

Should you have additional information or requests, please submit them to the committee (via Mrs. Haynes in Administration).

Yours sincerely,

Wayne L. Andrews, M.D., F.R.C.P.(C)  
Chairman  
Human Investigation Committee

mh

cc

Dr. A. R. Cooper

## **Appendix H**

### **Proposed Budget**

**Budget**

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**Personnel**

Research Nurse I (½ time)	
@ \$ 37397.08 / an.	12465.69
+ 20 % benefits	2493.14
Subtotal	14958.83
x 2 years	29917.66
 Data Entry Clerk (1 month)	
@ \$ 21964.24 / year	1830.35
+ 20 % benefits	366.07
total	2196.42
 Secretary I (1/10 time)	
@ \$ 24254.37 / year	2425.44
+ 20 % benefits	485.09
Subtotal	2910.53
x 2 years	5821.06
 Accounting Clerk I (1/10 time)	
@ \$ 23183.57 / year	2318.36
+ 20 % benefits	463.67
Subtotal	2782.03
x 2 years	5564.06
 Pharmacist II (1/10 time)	
@ \$ 41652.00 / year	4165.20
+ 20 % benefits	833.04
Subtotal	4998.24
x 2 years	9996.48
 <b>Total Personnel Budget</b>	<b><u>53495.68</u></b>

**Expendibles****Drugs and Drug Administration:**

Beclomethasone mdi's

80 patients

pediatricerochambers and masks

80 patients @ \$25.50

TO BE PROVIDED BY DRUG COMPANIES

2040.00

**Total Drugs and Drug Administration****2040.00****Materials and Supplies:**

Printing of consent forms, data  
    recording forms and parent  
    questionnaires

200.00

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Photocopying	40.00
<b>TOTAL MATERIALS AND SUPPLIES</b>	<b><u>240.00</u></b>
 <b>TOTAL EXPENDIBLES</b>	 <b><u>2280.00</u></b>
<u>Utility Services</u>	
Telephone long distance @ 300.00 / year	600.00
Postage @ 0.43 / letter	50.00
<b>TOTAL UTILITY SERVICES</b>	<b><u>650.00</u></b>
 <u>Travel</u>	
Principal and Co-investigators to travel to international meeting to present data	<b><u>2000.00</u></b>
 <u>Other</u>	
Publication 5 pages @ 75.00 / page	375.00
<b>TOTAL OTHER</b>	<b><u>475.00</u></b>
<b><u>TOTAL PROJECT BUDGET</u></b>	<b><u>\$58800.68</u></b>
 <b>ACTUAL FUNDING RECEIVED</b>	 <b>\$17 000.00</b>

## **Appendix I**

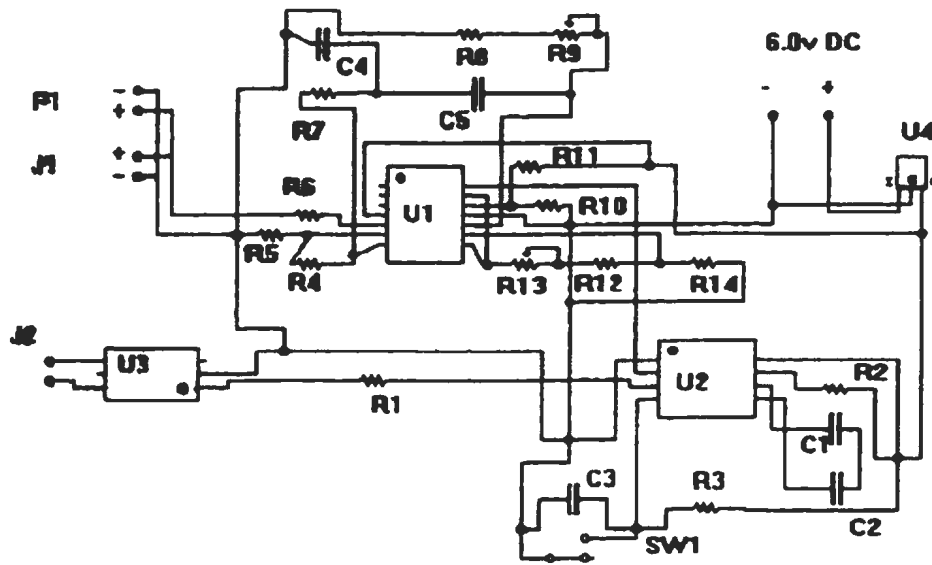
### **Circuit Diagram of Cough-Recorder**

**COUGH COUNTER - Parts List**

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<u>Circuit Designation</u>	<u>Part Number</u>	<u>Description</u>
U1	uA324	Quad Operational Amplifier Timer / Oscillator Solid State Relay +5v Voltage Regulator
U2	LM555	
U3	AQV201	
U4	7805	
C1, C3	10 uF	Electrolytic
C2, C4, C5	0.01 uF	
R1	270 Ohm	All Resistors are rated 5% and 1/8 watt
R2	10 MOhm	
R3	47 KOhm	
R4	1 MOhm	
R5, R6	100 Ohm	
R7, R12	6.8 KOhm	
R8	27 KOhm	
R9, R13	10 KOhm Potentiometers	
R10, R14	1 KOhm	
R11	22 KOhm	
J1, J2	1/8 inch Phono jack	
P1	1/8 inch Phono plug	
SW1	Momentary Switch, Push Button Normally Open	

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## **Appendix J**

### **Pilot Project Protocol, Consent Forms, and Human Investigation Committees Approval Letters**



**The Use Of Sound-triggered Audio-tape Recording  
to Count Coughing Paroxysms in the Pertussis Population:  
A Pilot Study**

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**PROTOCOL**

**I. PURPOSE:**

To generate statistics which can be used as a basis for designing a study of the effects of inhaled beclomethasone on the number of cough paroxysms per 24 hour period in the pediatric pertussis population.

**II. STUDY QUESTIONS:**

a) What is the inter-rater reliability of sound triggered audio-tape recording as a means of determining the number of coughing paroxysms per 24 hours in patients admitted with pertussis?

b) What are the mean and standard deviation of the number of coughing paroxysms in children with pertussis?

**III. SUBJECT SELECTION:**

The number of subjects required is 6 (six). Subjects will be selected from patients admitted to the hospital with a diagnosis of pertussis. Inclusion and exclusion criteria follow:

**Inclusion Criteria:**

-children with acute pertussis as defined by:

a) A positive Bordetella culture.

**OR**

b) A compatible clinical history and a positive Bordetella culture in a close contact (where close is defined as a member of the same household or daycare, or someone with whom there has been close contact (in the same room) for greater than 3 hours per day within 14 days prior to the onset of catarrhal symptoms).

-admitted to hospital

Exclusion Criteria:

-refusal to participate

#### IV. METHODS

After informed consent is obtained, subjects will be monitored using a sound-triggered audio-tape recording machine designed by the Janeway's electrical engineer for this purpose. The apparatus consists of a normal audio-tape recorder fitted with a switch which is activated by sound. When the child coughs, the recording mechanism is activated. It remains activated for three minutes after the onset of coughing. If the paroxysm lasts longer than three minutes, the machine reactivates with little perceived break. This avoids under- and over-counting of paroxysms. If the paroxysm is shorter than three minutes, the machine resets and waits for the next coughing episode. The only disadvantage of the apparatus is that it will also pick up extraneous noise in the child's room.

Monitoring will involve simply placing the microphone of the audio-tape recorder near the child's head and recording his or her coughs. The audiotape will be manually changed periodically to avoid missed data. Subjects will be recorded for the entire duration of their admission.

Once collected, audiotapes will be reviewed manually by both the primary investigator and the supervising staff and results will be compared for inter-rater reliability. Providing this is acceptable, the mean and standard deviation of the number of coughing paroxysms per 24 hour period will be calculated. This data will then be used to design another study to look at the effect of inhaled beclomethasone on the number of coughing paroxysms per 24 hour period.

#### V. ETHICS

a) Informed Consent

Informed consent will be obtained from parents or guardians of all study participants by the principal investigator or his delegate. A copy of the consent form is enclosed.

**b) Risk / Benefit Analysis**

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There are few, if any, risks associated with this intervention. Potential benefits include the provision of statistics which will allow the design of a future study on the use of steroids in pertussis, as well as the provision of a reliable research tool for counting the number of paroxysms of coughing in this population and other similar ones.

**c) Confidentiality**

While the use of audio-tape recorders which may record conversation, as well as the intended coughing spells, presents some concerns about invasion of privacy, similar situations are not uncommon in the pertussis population. Patients admitted with pertussis are routinely placed in rooms that are monitored with intercoms. These devices also are capable of picking up conversation.

To avoid any problems concerning this issue, parents will be told explicitly that conversation, as well as coughing, can be recorded by the machines and that any private conversations should be conducted outside the patient's room. Tapes will be marked only with the subject's code number, and the master code list will be kept under lock and key by the primary investigator. Tape reviewers will keep any information learned from reviewing the tapes in confidence.

**d) Cost to the System**

It is understood that patients will not be able to be admitted to the hospital solely for the purposes of this investigation.

FACULTY OF MEDICINE  
MEMORIAL UNIVERSITY OF NEWFOUNDLAND  
ST. JOHN'S, NEWFOUNDLAND, A1B 3X6

CONSENT TO PARTICIPATE IN BIOMEDICAL RESEARCH

Title: The Use of Sound triggered Audio-tape Recording to Count Coughing Paroxysms in Patients with Pertussis : A Pilot Study.

Investigators: Dr. Andrew Warren  
Dr. A.R. Cooper

Your child has been selected to participate in a research study. Participation in this study is entirely voluntary. You may decide not to allow your child to participate or may withdraw from the study at any time without affecting your child's normal treatment.

Confidentiality of information concerning participants will be maintained by the investigator. The investigator will be available during the study at all times should you have any problems or questions about the study.

Purpose

The purposes of this study are to test 1) the feasibility of using sound-triggered recording to count coughing episodes in patients with pertussis and 2) to determine the average and standard deviation of the number of coughs per 24 hours in this group of patients.

Procedures

If you agree to participate in the study, a special tape recorder will be placed in your child's room for the duration of his/her stay at the Janeway. Each time the child coughs the tape-recorder will be activated and the cough will be recorded. The tapes will later be reviewed by the investigator and the number of coughs per 24 hour period will be counted. Tapes will be marked and changed as necessary to ensure accurate data collection.

### Risks, Discomfort and Inconveniences

The study will not cause any risk or discomfort for your child whatsoever. The fact that the tape-recorder will also pick up and record normal conversation may, however represent some inconvenience. Any conversation accidentally recorded will be kept in strict confidence. 162

### Benefits

While there are no immediate benefits to subjects who participate, the development of sound triggered recording as an effective means of research monitoring may allow the testing of medicines which could be of benefit to other children with pertussis (whooping cough) in the future.

### Alternative Procedures or Treatment for Those Not Entering the Study

If you choose not to participate in the study your child will be monitored and treated in exactly the same way children with pertussis are usually treated. This may or may not involve placement in a room with an intercom to allow nursing staff to respond to coughing spells. Your refusal to participate in the research project will not affect your child's treatment in any way.

I, \_\_\_\_\_, the undersigned, agree to

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the participation of \_\_\_\_\_ (my child/  
ward/relative) in the research study described.

Any questions have been answered and I understand what is involved in the study. I realize that participation is voluntary and that there is no guarantee my child/ward/relative will benefit from his/her involvement. I acknowledge that a copy of this form has been offered to me.

\_\_\_\_\_  
Signature of Participant

\_\_\_\_\_  
Date

To be signed by investigator

To the best of my ability I have fully explained to the subject's parent/guardian the nature of this research study. I have invited questions and provided answers. I believe that the subject fully understands the implications and voluntary nature of the study.

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Signature of Investigator

---

Date

To locate the investigator you may page through the hospital's switchboard operator.

---

Signature of minor  
participant

---

Age

---

Relationship to  
participant named  
above



# Memorial

University of Newfoundland

Human Investigation Committee  
Office of Research and Graduate Studies (Medicine)  
Faculty of Medicine, The Health Sciences Centre

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21 February 1994

**Reference #94-11**

Dr. Andrew Warren  
Resident  
Janeway Child Health Centre  
St. John's, Nfld

Dear Dr. Warren:

At a meeting of the Human Investigation Committee held on February 10, 1994, your application entitled "A Pilot Study on the Use of Sound-Triggered Tape Recording to Count Cough Paroxysms in the Pertussis Population" was considered. The Committee recommended approval of your application subject to a notice being posted on the door warning that conversations in the room might be recorded. As well, one specific modification was requested to the consent form as outlined on the attached. Please send a copy of the revised consent form to the HIC office.

We take this opportunity to wish you every success with your research study.

Sincerely yours,

C. S. Mellor, MD, PhD, FRCP(C)  
Chairman  
Human Investigation Committee

c.c. Dr. K. M. W. Keough, Vice-President (Research)  
Dr. Wayne Andrews, Chairperson, Ethics Committee, Janeway  
Hospital  
Dr. Kevin Hogan, Medical Director, Janeway Hospital  
Dr. A. R. Cooper, Supervisor





**Reference #94-11**

The Committee requested the following modification to the consent form:

Page 2 - Alternate Procedures, Delete line 3 "This may or may not involve placement in a room with an intercom to allow nursing staff to respond to coughing spells."



*The Dr. Charles A.*

# Janeway Child Health Centre

JANEWAY PLACE, ST. JOHN'S, NEWFOUNDLAND CANADA A1A 1R8

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Dr. A. Warren and Dr. A. R. Cooper

Dear Drs. Warren and Cooper:

**Re: Project 288-94 - A Pilot Study on the Use of Sound-Triffered Tape  
Recording to Count Coughing Paroxysms in the Pertussis Population**

I am writing to advise you that your proposal was reviewed by the Janeway's Human Investigation Committee and that it is:

- ☒ approved
- ☐ approved with the following questions, observations or limits (see attached)
- ☐ deferred pending receipt of additional information (see attached)
- ☐ deferred pending your personal review of this proposal at the next Human Investigation Committee meeting.
- ☐ not approved.

Should you have additional information or requests, please submit them to the committee (via Mrs. Haynes in Administration).

Yours sincerely,

Wayne L. Andrews, M.D., F.R.C.P.(C)  
Chairman  
Human Investigation Committee

mh

cc Dr. A. R. Cooper





